Introduction and rationale

Benign hepatic tumors include a broad spectrum of regenerative and true neoplastic processes. Because of advances in imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI) as well as progress in immunohistochemistry, accurate diagnosis can now be made in a large percentage of patients without surgical laparotomy or resection.

This article will focus on the pathogenesis, diagnosis, and management of focal benign lesions of the liver. Many of these tumors present with typical features in various imaging studies. On occasions, biopsies are required and/or surgical removal is needed.

The most common benign hepatic tumors include cavernous hemangioma, focal nodular hyperplasia, hepatic adenoma, and nodular regenerative hyperplasia.

In the majority of cases of benign hepatic tumors, patients are asymptomatic, and no treatment is indicated. The main indication for treatment is the presence of significant clinical symptoms or suspicion of malignancy or fear of malignant transformation. ***(J Clin 2005).***

Benign hepatic tumors are increasingly reported with the widespread use of sensitive imaging studies and occasionally present significant diagnostic and therapeutic challenges. They usually occur in asymptomatic patients with or without underlying liver disease.

Using simple imaging techniques such as ultrasound (US), benign hepatic tumors can be categorized as solitary or multiple and as solid or cystic.

In general, a single imaging study is insufficient for a definitive diagnosis, and further studies may be necessary.

Most benign hepatic tumors follow a fairly indolent clinical course. However, some of them are associated with serious complications.

Thus, the understanding of clinical, radiologic, and pathologic characteristics of each tumor is important for accurate diagnosis and appropriate treatment of these tumors.

Differentiating benign liver lesions from cancers can sometimes be done by radiologic imaging studies alone. If the diagnosis is not clear, then often a liver biopsy is done to examine a sliver of the liver mass under the microscope. This allows the liver pathologist to determine the tissue diagnosis. It is helpful to compare the size of the lesion to prior imaging studies (if they exist), to determine if the mass is growing.

This article will review several benign hepatic tumors that are commonly encountered in adults. We will categorize them as solid or cystic tumors and describe key differential diagnostic criteria for each tumor. We will also propose a stepwise approach for diagnosis and treatment of asymptomatic patients with benign hepatic tumors.

"… because the liver is a source of many diseases,
and is a noble organ that serves many organs,
almost all of them: so it suffers, it is not a small
suffering, but a great and manifold one"

Theophrastus Bombastus von Hohenheim,
known as Paracelsus (1493_1541).

Aim of the work

To high light on:

1. Pathogenesis of different types of benign focal hepatic lesions.
2. Different approaches for diagnosis and therapy of these lesions.

Liver Anatomy and Function

The liver, the largest organ in the body, weighs *1200–1500g* and comprises *one-fiftieth* of the total adult body weight. It is relatively larger in infancy, comprising *one-eighteenth* of the birth weight. This is mainly due to a large left lobe.

Sheltered by the ribs in the right upper quadrant, the upper border lies approximately at the level of the nipples.

There are two anatomical lobes, the right being about six times the size of the left. Lesser segments of the right lobe are the caudate lobe on the posterior surface and the quadrate lobe on the inferior surface. The right and left lobes are separated anteriorly by a fold of peritoneum called the *falciform ligament*, posteriorly by the fissure for the *ligamentum venosum* and inferiorly by the fissure for the *ligamentum teres.*

The liver has a double blood supply. The *portal vein* brings venous blood from the intestines and spleen and the *hepatic artery*, coming from the coeliac axis, supplies the liver with arterial blood. These vessels enter the liver through a fissure, the *porta hepatis*, which lies far back on the inferior surface of the right lobe. Inside the porta, the portal vein and hepatic artery divide into branches to the right and left lobes, and the right and left hepatic bile ducts join to form the common hepatic duct.

The *hepatic nerve* plexus contains fibres from the sympathetic ganglia T7–T10, which synapse in the coeliac plexus, the right and left vagi and the right phrenic nerve. It accompanies the hepatic artery and bile ducts into their finest ramifications, even to the portal tracts and hepatic parenchyma ***(Adler et al; 1999).***

The *ligamentum venosum*, a slender remnant of the ductus venosus of the fetus, arises from the left branch of the portal vein and fuses with the inferior vena cava at the entrance of the left hepatic vein. The

ligamentum teres, a remnant of the umbilical vein of the fetus, runs in the free edge of the falciform ligament from the umbilicus to the inferior border of the liver and joins the left branch of the portal vein. Small veins accompanying it connect the portal vein with veins around the umbilicus. These become prominent when the portal venous system is obstructed inside the liver ***(Marieb et al; 2001).***

The *venous drainage* from the liver is into the right and left hepatic veins which emerge from the back of the liver and at once enter the inferior vena cava very near its point of entry into the right atrium.

Lymphatic vessels terminate in small groups of glands around the porta hepatis. Efferent vessels drain into glands around the coeliac axis. Some superficial hepatic lymphatics pass through the diaphragm in the falciform ligament and finally reach the mediastinal glands. Another group accompanies the inferior vena cava into the thorax and ends in a few small glands around the intrathoracic portion of the inferior vena cava. The inferior vena cava makes a deep groove to the right of the caudate lobe about 2 cm from the mid-line.

The gallbladder lies in a fossa extending from the inferior border of the liver to the right end of the porta hepatis.

The liver is completely covered with peritoneum, except in three places. It comes into direct contact with the diaphragm through the *bare area* which lies to the right of the fossa for the inferior vena cava. The other areas without peritoneal covering are the fossae for the inferior vena cava and gallbladder.

The liver is kept in position by peritoneal ligaments and by the intrabdominal pressure transmitted by the tone of the muscles of the abdominal wall.

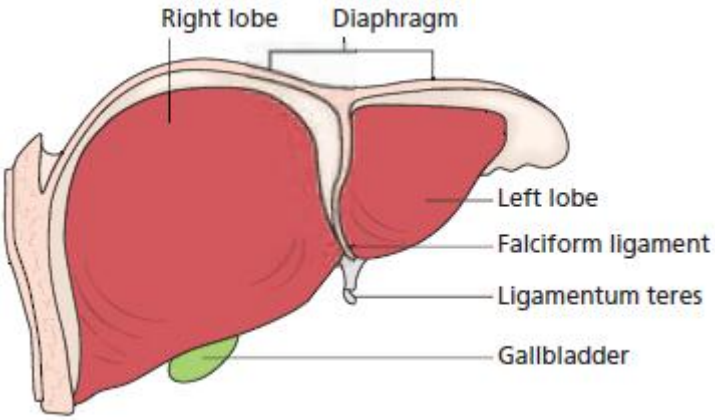


Fig. 1. **Anterior view of the liver.**

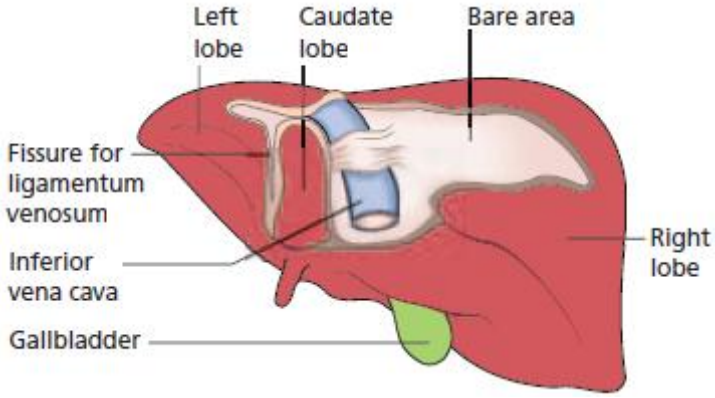


Fig. 2. **Posterior view of the liver.**

Functional anatomy: *sectors and segments*:

Based on the external appearances described above, the liver has a right and left lobe separated along the line of insertion of the falciform ligament. This separation, however, does not correlate with blood supply or biliary drainage. A functional anatomy is now recognized based upon studies of vascular and biliary casts made by injecting vinyl into the vessels and bile ducts. This classification correlates with that seen by imaging techniques.

The main portal vein divides into right and left branches and each of these supplies two further subunits (variously called sectors). The sectors on the right side are anterior and posterior and, in the left lobe, medial and lateral—giving a total of four sectors.

Using this definition, the right and left side of the liver are divided not along the line of the falciform ligament, but along a slightly oblique line to the right of this, drawn from the inferior vena cava above to the gallbladder bed below. The right and left side are independent with regard to portal and arterial blood supply, and bile drainage. Three plains separate the four sectors and contain the three major hepatic vein branches.

Closer analysis of these four hepatic sectors produces a further subdivision into segments. The right anterior sector contains segments V and VIII; right posterior sector, VI and VII; left medial sector, IV; left lateral sector, segments II and III.

There is no vascular anastomosis between the macroscopic vessels of the segments but communications exist at sinusoidal level. Segment I, the equivalent of the caudate lobe, is separate from the other segments and does not derive blood directly from the major portal branches or drain by any of the three major hepatic veins.

This functional anatomical classification allows interpretation of radiological data and is of importance to the surgeon planning a liver resection. There are wide variations in portal and hepatic vessel anatomy which can be demonstrated by spiral computed tomography (CT) and magnetic resonance imaging (MRI) reconstruction ***(Feray et al;1994).***

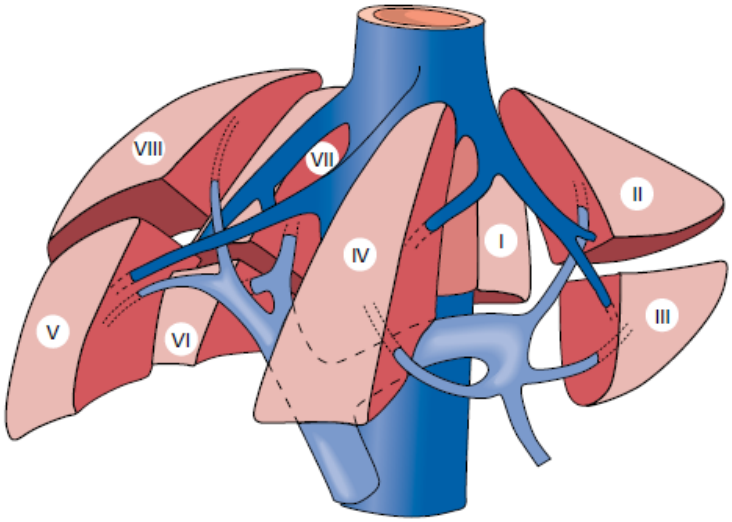


Fig. 3 **Schematic representation of the functional anatomy of the liver. Three main hepatic veins (dark blue) divide the liver into four sectors, each of them receiving a portal pedicle; hepatic veins and portal veins are intertwined as the fingers of two hands [5].**

Anatomy of the biliary tract:

The right and left hepatic ducts emerge from the liver and unite in the porta hepatis to form the common hepatic duct. This is soon joined by the cystic duct from the gallbladder to form the common bile duct.

The common bile duct runs between the layers of the lesser omentum, lying anterior to the portal vein and to the right of the hepatic artery. Passing behind the first part of the duodenum in a groove on the back of the head of the pancreas, it enters the second part of the duodenum.

The duct runs obliquely through the postero-medial wall, usually joining the main pancreatic duct to form the *ampulla of Vater* (***1720***). The ampulla makes the mucous membrane bulge inwards to form an eminence: the duodenal papilla. In about 10–15% of subjects the bile and pancreatic ducts open separately into the duodenum.

The dimensions of the common bile duct depend on the technique used. At operation it is about 0.5–1.5cm in diameter. Using *ultrasound* the values are less, the common bile duct being 2–7mm, with values greater than 7mm being regarded as abnormal. Using *endoscopic cholangiography*, the duct diameter is usually less than 11mm, although after cholecystect- omy it may be more in the absence of obstruction.

The duodenal portion of the common bile duct is surrounded by a thickening of both longitudinal and circular muscle fibres derived from the intestine. This is called the *sphincter of Oddi* (***1887***).

The *gallbladder* is a pear-shaped bag 9cm long with a capacity of about 50 ml. It always lies above the transverse colon, and is usually next to the duodenal cap overlying, but well anterior to, the right renal shadow.

Any decrease in concentrating power is accompanied by reduced distensibility. The fundus is the wider end and is directed anteriorly; this

is the part palpated when the abdomen is examined. The body extends into a narrow neck which continues into the cystic duct.

The valves of Heister are spiral folds of mucous membrane in the wall of the cystic duct and neck of the gallbladder. *Hartmann's pouch* is a sacculation at the neck of the gallbladder; this is a common site for a gallstone to lodge.

The wall consists of a musculo-elastic network without definite layers, the muscle being particularly well developed in the neck and fundus. The mucous membrane is in delicate closely woven folds; instead of glands there are deep indentations of mucosa, the crypts of *Luschka*, which penetrate into the muscular layer.There is no submucosa or muscularis mucosae.

The *Rokitansky–Aschoff* sinuses are branching evaginations from the gallbladder lumen lined by mucosa reaching into the muscularis of the gallbladder. They play an important part in acute cholecystitis and gangrene of the gallbladder wall.

***Blood supply* :** The gallbladder receives blood from the cystic artery. This branch of the hepatic artery is large, tortuous and variable in its anatomical relationships. Smaller blood vessels enter from the liver through the gallbladder fossa. The venous drainage is into the cystic vein and thence into the portal venous system.

The arterial blood supply to the supra-duodenal bile duct is generally by two main (axial) vessels which run beside the bile duct. These are supplied predominantly by the retro-duodenal artery from below, and the right hepatic artery from above, although many other vessels contribute. This pattern of arterial supply would explain why vascular damage results in bile duct structuring ***(Charlton et al; 1998).***

Lymphatics: There are many lymphatic vessels in the submucous and subperitoneal layers. These drain through the cystic gland at the neck

of the gallbladder to glands along the common bile duct, where they anastomose with lymphatics from the head of the pancreas.

Nerve supply: The gallbladder and bile ducts are liberally supplied with nerves, from both the parasympathetic and the sympathetic system.

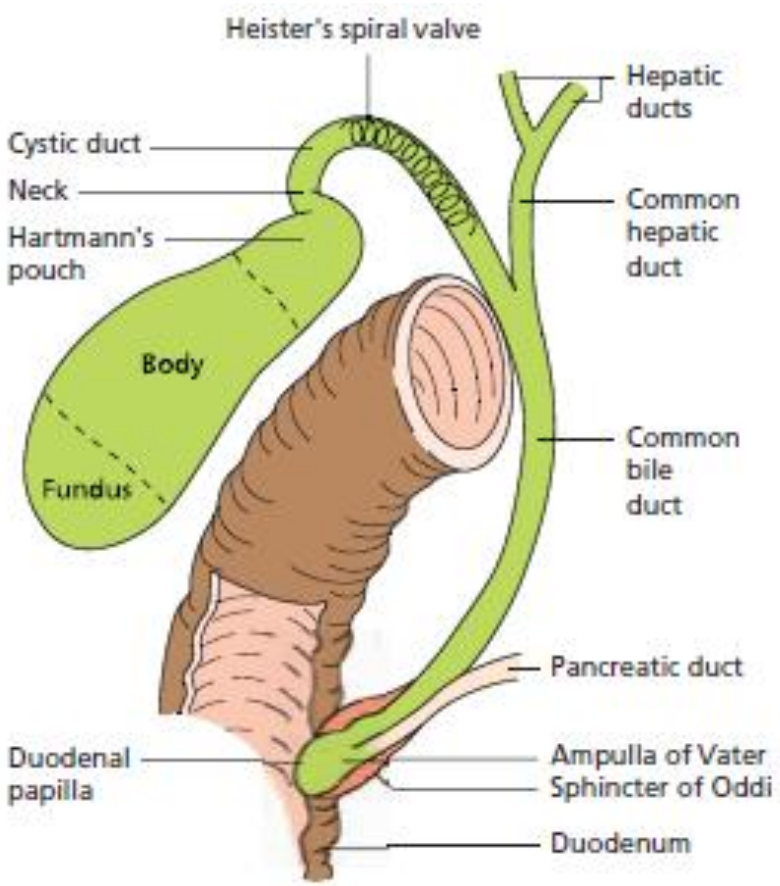


Fig. 4. **Gallbladder and biliary tract.**

Hepatic morphology:

Kiernan (1833) introduced the concept of hepatic lobules as the basic architecture. He described circumscribed pyramidal lobules consisting of a central tributary of the hepatic vein and at the periphery a portal tract containing the bile duct, portal vein radicle and hepatic artery branch. Columns of liver cells and blood-containing sinusoids extend between these two systems.

Stereoscopic reconstructions and scanning electron microscopy have shown the human liver as columns of liver cells radiating from a central vein, and interlaced in orderly fashion by sinusoids.

The liver tissue is pervaded by two systems of tunnels, the portal tracts and the hepatic central canals which dovetail in such a way that they never touch each other; the terminal tunnels of the two systems are separated by about 0.5 mm. As far as possible the two systems of tunnels run in planes perpendicular to each other.

The sinusoids are irregularly disposed, normally in a direction perpendicular to the lines connecting the central veins. The terminal branches of the portal vein discharge their blood into the sinusoids and the direction of flow is determined by the higher pressure in the portal vein than in the central vein.

The central hepatic canals contain radicles of the hepatic vein and their adventitia. They are surrounded by a limiting plate of liver cells.

The *portal triads* (syn. portal tracts, *Glisson's capsule*) contain the portal vein radicle, the hepatic arteriole and bile duct with a few round cells and alittle connective tissue. They are surrounded by a limiting plate of liver cells. *Portal dyads* are as frequent as triads, with the portal vein being the most frequently absent element.

Within each linear centimetre of liver tissue obtained at biopsy there are usually two interlobular bile ducts, two hepatic arteries and one

portal vein per portal tract, with six full portal triads ***(Berenguer et al; 2000).***

The liver has to be divided functionally. Traditionally, the unit is based on a central hepatic vein and its surrounding liver cells. However, *Rappaport* ***(Couteil et al; 1997)*** envisages a series of functional acini, each centred on the portal triad with its terminal branch of portal vein, hepatic artery and bile duct. These interdigitate, mainly perpendicularly, with terminal hepatic veins of adjacent acini. The circulatory peripheries of acini (adjacent to terminal hepatic veins) suffer most from injury whether viral, toxic or anoxic. Bridging necrosis is located in this area.

The regions closer to the axis formed by afferent vessels and bile ducts survive longer and may later form the core from which regeneration will proceed. The contribution of each acinar zone to liver cell regeneration depends on the acinar location of damage ***(Couteil et al; 1997)***.

The liver cells (hepatocytes) comprise about 60% of the liver. They are polygonal and approximately 30mm in diameter. The nucleus is single or, less often, multiple and divides by mitosis.

The lifespan of liver cells is about 150 days in experimental animals. The hepatocyte has three surfaces: *one* facing the sinusoid and space of Disse, *the second* facing the canaliculus and *the third* facing neighbouring hepatocytes. There is no basement membrane.

The sinusoids are lined by endothelial cells. Associated with the sinusoids are the phagocytic cells of the reticulo-endothelial system (Kupffer cells), and the hepatic stellate cells, which have also been called fatstoring cells, Ito cells and lipocytes.

There are approximately 202·103 cells in each milligram of normal human liver, of which 171·103 are parenchymal and 31·103 littoral (sinusoidal, including Kupffer cells).

The space of Disse is a tissue space between hepatocytes and sinusoidal endothelial cells. The hepatic lymphatics are found in the peri-portal connective tissue and are lined throughout by endothelium. Tissue fluid seeps through the endothelium into the lymph vessels.

The branch of the hepatic arteriole forms a plexus around the bile ducts and supplies the structures in the portal tracts. It empties into the sinusoidal network at different levels. There are no direct hepatic arteriolar–portal venous anastomoses.

The excretory system of the liver begins with the bile canaliculi. These have no walls but are simply grooves on the contact surfaces of liver cells. Their surfaces are covered by microvilli. The plasma membrane is reinforced by micro-filaments forming a supportive cytoskeleton.

The canalicular surface is sealed from the rest of the intercellular surface by junctional complexes including tight junctions, gap junctions and desmosomes. The intralobular canalicular network drains into thin-walled terminal bile ducts or ductules (cholangioles, canals of Hering) lined with cuboidal epithelium. These terminate in larger (interlobular) bile ducts in the portal canals.They are classified into small (less than 100mm in diameter), medium (about 100mm) and large (more than100mm).

Physiology of the liver:

The various functions of the liver are carried out by the liver cells or hepatocytes.

The liver produces and excretes bile required for food digestion. Some of the bile drains directly into the duodenum, and some is stored in the gallbladder.

- ***The liver performs several roles in carbohydrate metabolism:***

-Gluconeogenesis (the formation of glucose from certain amino acids, lactate or glycerol)

-Glycogenolysis (the formation of glucose from glycogen)

-Glycogenesis (the formation of glycogen from glucose)

-The breakdown of insulin and other hormones

- ***The liver also performs several roles in lipid metabolism:***

-Cholesterol synthesis

-The production of triglycerides (fats).

The liver produces coagulation factors I (fibrinogen), II (prothrombin), V, VII, IX, and XI, as well as protein C, protein S and antithrombin.

- The liver breaks down hemoglobin (bile pigments are its metabolites), toxic substances and most medicinal products. This sometimes results in toxication, when the metabolite is more toxic than its precursor.
- The liver converts ammonia to urea.
- The liver stores a multitude of substances, including glucose in the form of glycogen, vitamin B12, iron, and copper.

Classification of liver diseases:

I- Toxic injury to the liver induced by Drugs.

II- Industrial and environmental toxicity.

III- Alcoholic liver disease.

IV-Postoperative hepatic dysfunction.

V- Primary biliary cirrhosis.

VI-Infectious agents and parasites:

- Hepatitis virus.
- Bacterial and other pathogenic agents.
- Parasites.

VII- Tumors:

- Primary malignant tumors.
- Metastatic malignant tumors.
- Benign hepatic tumors.
- Tumor-like lesion.

VIII- Inherited:

- Wilson's disease.
- Hemochromatosis.
- Inborn errors.
- Alpha-1-antitrypsin deficiency.
- Cyst.

IX- Immune & Autoimmune disorder.

I) Drugs and the liver:

Drug metabolism:

The liver is the major site of drug metabolism. Drugs are converted from fat-soluble to water-soluble substances that can be excreted in the urine or bile. This metabolism of drugs is mediated by a group of mixed-function enzymes.

Drug hepatotoxicity:

Many drugs impair liver function, and drugs should always be considered as a cause when mildly abnormal liver tests are found. Damage to the liver by drugs is usually classified as being either predictable (or dose-related) or non-predictable (not dose-related).

This classification should not be used rigidly, as there is considerable overlap and at least six mechanisms may be involved in the production of damage:(1) disruption of intracellular calcium homeostasis; (2) disruption of bile canalicular transport mechanisms; (3) formation of non-functioning adducts (enzyme-drug) which may then (4) present on the surface of the hepatocyte as new immunogens (attacked by T cells); (5) induction of apoptosis; (6) inhibition of mitochondrial function, which prevents fatty acid metabolism, and accumulation of both lactate and reactive oxygen species.

The predominant mechanism or combination of mechanisms determines the type of liver injury, i.e. hepatitic, cholestatic or immunological (skin rashes, fever and arthralgia (serum-sickness syndrome). Eosinophilia and circulating immune complexes and antibodies may occasionally be detected ***(Bissell et al; 2001).***

When a small amount of hepatotoxic drug whose effect is dose-dependent (e.g. paracetamol) is ingested, a large proportion of it

undergoes conjugation with glucuronide and sulphate, whilst the remainder is metabolized by microsomal enzymes to produce toxic derivatives that are immediately detoxified by conjugation with glutathione. If larger doses are ingested, the former pathway becomes saturated and the toxic derivative is produced at a faster rate. Once the hepatic glutathione is depleted, large amounts of the toxic metabolite accumulate and produce damage ***(Kaplowitz et al; 2002).***

The 'predictability' of drugs to produce damage can, however, be affected by metabolic events preceding their ingestion. For example, chronic alcohol abusers may become more susceptible to liver damage because of the enzyme-inducing effects of alcohol, or ill or starving patients may become susceptible because of the depletion of hepatic glutathione produced by starvation.

Many other factors such as environmental or genetic effects may be involved in determining the 'susceptibility' of certain patients to certain drugs ***(Navarro et al; 2006).***

Hepatitic damage:

The diagnosis of these conditions is usually by exclusion of other causes. Most reactions occur within 3 months of starting the drug. Monitoring liver biochemistry in patients on long-term treatment, such as antituberculosis therapy, is advisable. If a drug is suspected of causing hepatic damage it should be stopped immediately.

Liver biopsy is of limited help in confirming the diagnosis, but occasionally hepatic eosinophilia or granulomas may be seen. Diagnostic challenge with subtherapeutic doses of the drug is sometimes required after the liver biochemistry has returned to normal, to confirm the diagnosis ***(Maddrey WC; 2005).***

Drug prescribing for patients with liver disease:

The metabolism of drugs is impaired in severe liver disease (with jaundice and ascites) as the removal of many drugs depends on liver blood flow and the integrity of the hepatocyte.

In general, therefore, the effect of drugs is prolonged by liver disease and also by cholestasis. This is further accentuated by portosystemic shunting, which diminishes the first-pass extraction of drugs. With hypoproteinaemia there is decreased protein binding of some drugs, and bilirubin competes with many drugs for the binding sites on serum albumin. In patients with portosystemic encephalopathy, care must be taken in prescribing drugs with a central depressant action ***(Lee WM; 2003)***

II) Industrial and Environmental Toxin:

Liver injury may follow the inhalation, ingestion, or parenteral administration of a number of pharmacologic and chemical agents. These include industrial toxins (e.g., carbon tetrachloride, trichloroethylene, and yellow phosphorus), the heat-stable toxic bicyclic octapeptides of certain species of Amanita and Galerina (hepatotoxic mushroom poisoning).

Agents producing toxic hepatitis are generally systemic poisons or are converted in the liver to toxic metabolites. The direct hepatotoxins result in morphologic abnormalities that are reasonably characteristic and reproducible for each toxin ***(Stickel et al;2005).***

For example, carbon tetrachloride and trichloroethylene characteristically produce a centrilobular zonal necrosis, whereas yellow phosphorus poisoning typically results in periportal injury. The hepatotoxic octapeptides of Amanita phalloides usually produce massive hepatic necrosis; the lethal dose of the toxin is ~10 mg, the amount found in a single deathcap mushroom ***(Browning JD;2006).***

Liver injury, which is often only one facet of the toxicity produced by the direct hepatotoxins, may go unrecognized until jaundice appears**.**

III) Alcoholic Liver Diseases:

Chronic and excessive alcohol ingestion is one of the major causes of liver disease. The pathology of alcoholic liver disease comprises three major lesions, with the injury rarely existing in a pure form: (1) fatty liver, (2) alcoholic hepatitis, and (3) cirrhosis***(Fauci et al;2008).***

Etiology and Pathogenesis:

Quantity and duration of alcohol intake are the most important risk factors involved in the development of alcoholic liver disease.

Ethanol is metabolized in the liver by two pathways, resulting in an increase in the NADH/NAD ratio. The altered redox potential results in increased hepatic fatty acid synthesis with decreased fatty acid oxidation, both events leading to hepatic accumulation of fatty acid that is then esterified to glycerides.

The changes in oxidation-reduction also impair carbohydrate and protein metabolism and are the cause of the centrilobular necrosis of the hepatic acinus typical of alcohol damage.

Acetaldehyde is formed by the oxidation of ethanol and its effect on hepatic proteins may well be a factor in producing liver cell damage. The exact mechanism of alcoholic hepatitis and cirrhosis is unknown, but since only 10-20% of people who drink heavily will suffer from cirrhosis, a genetic predisposition is suggested. Immunological mechanisms have also been proposed.

Alcohol can enhance the effects of toxic metabolites of drugs (e.g. paracetamol) on the liver, as it induces microsomal metabolism via the microsomal ethanol oxidizing system (MEOS)***(Kumar et al;2007).***

IV) Viral Hepatitis:

A. Acute Hepatitis :

Acute viral hepatitis is a systemic infection affecting the liver predominantly. Almost all cases of acute viral hepatitis are caused by one of five viral agents: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), the HBV-associated delta agent or hepatitis D virus (HDV), and hepatitis E virus (HEV). Other transfusion-transmitted agents, e.g., "hepatitis G" virus and "TT" virus, have been identified but do not cause hepatitis ***(Adler et al; 1999).***

All these human hepatitis viruses are RNA viruses, except for hepatitis B, which is a DNA virus. Although these agents can be distinguished by their molecular and antigenic properties, all types of viral hepatitis produce clinically similar illnesses. These range from asymptomatic and inapparent to fulminant and fatal acute infections common to all types, on the one hand, and from subclinical persistent infections to rapidly progressive chronic liver disease with cirrhosis and even hepatocellular carcinoma, common to the bloodborne types (HBV, HCV, and HDV) ***(Feray et al; 1994).***

B.Chronic Hepatitis:

Chronic hepatitis represents a series of liver disorders of varying causes and severity in which hepatic inflammation and necrosis continue for at least 6 months. Milder forms are nonprogressive or only slowly progressive, while more severe forms may be associated with scarring and architectural reorganization, which, when advanced, lead ultimately to cirrhosis.

Several categories of chronic hepatitis have been recognized. These include chronic viral hepatitis, drug-induced chronic hepatitis, and

autoimmune chronic hepatitis. In many cases, clinical and laboratory features are insufficient to allow assignment into one of these three categories; these "idiopathic" cases are also believed to represent autoimmune chronic hepatitis ***(Berenguer et al; 2000).***

Finally, clinical and laboratory features of chronic hepatitis are observed occasionally in patients with such hereditary/metabolic disorders as Wilson's disease (copper overload) and even occasionally in patients with alcoholic liver injury . Although all types of chronic hepatitis share certain clinical, laboratory, and histopathologic features, chronic viral and chronic autoimmune hepatitis are sufficiently distinct to merit separate discussions.

V) Cirrhosis and Its Complications:

Cirrhosis is a condition that is defined histopathologically and has a variety of clinical manifestations and complications, some of which can be life-threatening.

In the past, it has been thought that cirrhosis was never reversible; however, it has become apparent that when the underlying insult that has caused the cirrhosis has been removed, there can be reversal of fibrosis. This is most apparent with the successful treatment of chronic hepatitis C; however, reversal of fibrosis is also seen in patients with hemochromatosis who have been successfully treated and in patients with alcoholic liver disease who have discontinued alcohol use.

Regardless of the cause of cirrhosis, the pathologic features consist of the development of fibrosis to the point that there is architectural distortion with the formation of regenerative nodules. This results in a decrease in hepatocellular mass, and thus function, and an alteration of blood flow ***(Dodd et al; 1999).***

The induction of fibrosis occurs with activation of hepatic stellate cells, resulting in the formation of increased amounts of collagen and other components of the extracellular matrix.

Clinical features of cirrhosis are the result of pathologic changes and mirror the severity of the liver disease. Most hepatic pathologists provide an assessment of grading and staging when evaluating liver biopsy samples. These grading and staging schemes vary between disease states and have been developed for most conditions, including chronic viral hepatitis, nonalcoholic fatty liver disease, and primary biliary cirrhosis.

Advanced fibrosis usually includes bridging fibrosis with nodularity designated as stage 3 and cirrhosis designated as stage 4. Patients who have cirrhosis have varying degrees of compensated liver function, and clinicians need to differentiate between those who have stable, compensated cirrhosis and those who have decompensated cirrhosis. Patients who have developed complications of their liver disease and have become decompensated should be considered for liver transplantation. Many of the complications of cirrhosis will require specific therapy.

Portal hypertension is a significant complicating feature of decompensated cirrhosis and is responsible for the development of ascites and bleeding from esophagogastric varices, two complications that signify decompensated cirrhosis.

Loss of hepatocellular function results in jaundice, coagulation disorders, and hypoalbuminemia and contributes to the causes of portosystemic encephalopathy. The complications of cirrhosis are basically the same regardless of the etiology.

Nonetheless, it is useful to classify patients by the cause of their liver disease, patients can be divided into broad groups with alcoholic cirrhosis, cirrhosis due to chronic viral hepatitis, biliary cirrhosis, and other less-common causes such as cardiac cirrhosis, cryptogenic cirrhosis, and other miscellaneous causes.

VI) Genetic and Metabolic Diseases Affecting the Liver:

There are a number of disorders of the liver that fit within the categories of genetic and metabolic disorders. Inherited disorders include hemochromatosis, Wilson disease, $_1$ antitrypsin ($_1$AT) deficiency, and cystic fibrosis.

Hemochromatosis is the most common disorder affecting Caucasian populations, with the genetic susceptibility for the disease being identified in 1 in 250 individuals ***(Lanza, R. P. 2000)*** , but does not have to be inherited.

Hemochromatosis is a condition in which too much iron is contained in the body. Chronic hemochromatosis can lead to cirrhosis, cancer, impotence, and heart problems. Iron damages the body through its promotion of oxidation, increasing the level of free radicals in the body.

Harmful levels of iron can be accumulated in the body simply by eating too much of the wrong foods and supplements. The human body uses approximately 1 to 2 milligrams of iron daily. However, the average diet contains between 10 and 20 milligrams of iron ***(Palmer, M. 2000).*** Furthermore, iron is not expelled from the body easily.

In hemochromatosis, the body cannot absorb iron as effectively, and also cannot detect when iron levels are too high. This excess iron is then absorbed into the body's organs, particularly the liver.

Hemochromatosis also can co-exist along with other liver problems, making matters much worse for the patient.

Hemochromatosis is treated by lowering the level of iron in the body. The most common method is via phlebotomies. A phlebotomy is purposefully removing blood from the body, typically using a catheter, and discarding the blood. This must be done weekly over a long period of time to eliminate high levels of iron – perhaps years. For example, to deplete 25 grams of blood, it would take two years of weekly phlebotomies ***(Qi Z, et al. 1999).***

Diet is also very important to patients with hemochromatosis. Iron needs to be kept to a minimum, as well as alcohol and medications that may do further damage to the liver.

Over the past 10 years, it has become increasingly apparent that nonalcoholic fatty liver disease (NAFLD) is the most common cause of elevated liver enzymes found in the U.S. population. With the obesity epidemic in the United States, it is estimated that 20% of the population may have abnormal liver enzymes on the basis of NAFLD and 3% may have nonalcoholic steatohepatitis (NASH). Infiltrative disorders of the liver are relatively rare.

VII) Hepatic tumors:

I) Benign Hepatic tumors:

A. Focal benign Hepatic tumors:

- **Solid:**
  - Hemangioma.
  - Focal nodular hyperplasia.
  - Adenoma.
  - Macroregenerative nodule.
  - Focal fatty change.
  - Intrahepatic bile duct adenoma.
  - Mesenchymal hamartoma.
  - Lipomatous tumor.
  - Inflammatory pseudotumor.
  - Dysplastic nodules.
- **Cystic** :
  - Simple hepatic cyst.
  - congenital hepatic cyst.
  - Hepatic abscess (pyogenic & amoebic).
  - hydatid cyst (Echinococcal).
  - Biliary cystadenoma.
  - Choledochal cyst.
  - Caroli disease.

B. Diffuse benign Hepatic tumors:

- **Solid:**
  - Hemangioma.
  - Focal nodular hyperplasia.
  - Adenoma.
  - Macroregenerative nodule.
  - Focal fatty change.
  - Nodular regenerative hyperplasia.
- **Cyctic** :
  - Polycystic liver disease
  - Echinococcal cyst
  - Peliosis hepatis
  - Von Meyenburg complexes

II) Malignant Hepatic tumors:

A. Primary:

- Lymphoma
- Cholangiocarcinoma
- H.C.C

B. Secondary:

- Metastasis: particularly from the gastrointestinal tract, breast or bronchus.

We will first discuss in short the malignant types.

A) Malignant tumors:

I)Hepatocellular carcinoma (HCC):

Hepatocellular carcinoma (HCC) is one of the 10 most common cancers world-wide. Hepatocellular carcinoma (HCC) is a primary malignancy of the hepatocyte, generally leading to death within 6-20 months.

Aetiology:

Carriers of ***HBV*** and ***HCV*** have an extremely high risk of developing HCC. In areas where HBV is prevalent, 90% of patients with this cancer are positive for the hepatitis B virus. Cirrhosis is present in over 80% of these patients ***(DeVita et al; 2008).***

The development of HCC is related to the integration of viral HBV DNA into the genome of the host hepatocyte and possibly the degree of viral replication.

The risk of HCC in HCV is as high as or higher than in HBV despite no viral integration***(El-Serag et al; 2000).*** Primary liver cancer is also associated with other forms of cirrhosis, such as alcoholic cirrhosis and haemochromatosis.

Males are affected more than females; Hepatocellular carcinoma is the fifth most common cancer in men and the eighth most common cancer in women worldwide ***(Bosch et al; 2004).***

Patients with hemochromatosis, especially in the presence of cirrhosis, are at an increased risk of developing hepatocellular carcinoma.

Other suggested aetiological factors are aflatoxin (a metabolite of a fungus found in groundnuts) and androgenic steroids, and there is a weak association with the contraceptive pill.

Pathology

The tumour is either single or occurs as multiple nodules throughout the liver. Histologically it consists of cells resembling hepatocytes. It can metastasize via the hepatic or portal veins to the lymph nodes, bones and lungs.

Clinical features:

Patients generally present with symptoms of advancing cirrhosis.

- Pruritus.
- Jaundice.
- Splenomegaly.
- Variceal bleeding .
- Cachexia .
- Increasing abdominal girth (portal vein occlusion by thrombus with rapid development of ascites).
- Hepatic encephalopathy.
- Right upper quadrant pain (uncommon).

Physical

- Jaundice.
- Ascites.
- Hepatomegaly (enlarged, irregular, tender liver).
- Alcoholic stigmata (Dupuytren contracture, spider angiomata).
- Asterixis.
- Pedal edema.
- Periumbilical collateral veins.
- Enlarged hemorrhoidal veins.

Differential Diagnoses

- Cholangiocarcinoma.
- Cirrhosis.
- Hepatocellular Adenoma.

Other Problems to Be Considered

- Dysplastic nodules in cirrhosis.
- Fibrous nodular hyperplasia.
- Metastatic disease.
- Primary hepatic lymphoma.

Investigations:

❖ **<u>Laboratory Studies</u>:**

- Expect total bilirubin, aspartate aminotransferase (AST), alkaline phosphatase, albumin, and prothrombin time to show results consistent with cirrhosis.
- Alpha-fetoprotein (AFP) is elevated in 75% of cases the level of elevation correlates inversely with prognosis.

An elevation of greater than 400 ng/mL predicts for hepatocellular carcinoma with specificity greater than 95%. In the setting of a growing mass, cirrhosis, and the absence of acute hepatitis, many centers use a level greater than 1000 ng/mL as presumptive evidence of hepatocellular carcinoma (without biopsy). Alpha-fetoprotein (AFP) is inadequate for screening purposes because of the high rate of false positives in active hepatitis; it only begins to rise when vascular invasion occurs ***(Peng et al; 2004).***

❖ **Imaging Studies:**

- ***Ultrasonography*** is the least expensive choice for screening, but it is highly operator-dependent. A suspicious lesion on a sonogram generally requires additional imaging studies to confirm the diagnosis and the stage of the tumor. Sensitivity of ultrasonography for detection of small nodules is low. An advantage is that *Doppler imaging* can be performed at the same time to determine the patency of the portal vein.
- ***CT scanning*** (triphasic technique) (ie, without contrast, then with early [arterial] and late [portal] imaging). The addition of arterial phase imaging to conventional CT scanning increases the number of tumor nodules detected. Unfortunately, in nodular cirrhotic livers, the sensitivity of CT scanning for detecting hepatocellular carcinoma is low. CT scanning has the added benefit of detecting extrahepatic disease, especially lymphadenopathy.
- ***MRI*** may detect smaller lesions and can also be used to determine flow in the portal vein. However, in patients with nodular cirrhotic livers, MRI has been shown to have better sensitivity and specificity.
- ***Angiography*** shows characteristic tumor blush in hepatocellular carcinoma lesions. Angiography is still used for chemoembolization, one of the treatment options for hepatocellular carcinoma.

❖ **A liver biopsy**, particularly under ultrasonic guidance may be performed for diagnosis, but is increasingly less used as imaging techniques show characteristic appearances and because seeding along the biopsy tract can occur.

Treatment:

* Surgical resection is occasionally possible.
* Small tumours in patients with cirrhosis do well with liver transplantation.
* Chemotherapy and radiotherapy are unhelpful, but chemoembolization and probably embolization alone in selected patients prolong survival.

Prognosis:

Overall prognosis for survival depends on the extent of cirrhosis and tumor stage, which then determine the appropriate treatment. Patients able to undergo a curative resection have a median survival of as long as 4 years; patients who present when they are too ill to be treated have a median survival of 3 months ***(Stuart et al; 1996).***

Follow-up:

Monitor the progression of disease or adequacy of treatment with imaging studies every 2-3 months and LFTs and AFP monthly or as appropriate for the stage of disease and patient's performance status. These interventions, however, have little or no impact on prognosis for survival and therefore should be performed in accordance with the patient's functional status.

Prevention:

Persistent HBV infection, usually acquired after perinatal infection, is a high risk factor for HCC in many parts of the world, such as South East Asia. Widespread vaccination against HBV is being used and this has shown a reduction in the annual incidence of HCC in Taiwan ***(Bosch et al; 2004).***

II) Cholangiocarcinoma:

Cholangiocarcinomas (CCCs) are malignancies of the biliary duct system that may originate in the liver and extrahepatic bile ducts, which terminate at the ampulla of Vater ***(Douglass et al;1993&Lake et al;1993&Lotze et al;1993&de Groen et al;1999).***

CCCs are encountered in 3 geographic regions:

- ***Intrahepatic***,
- ***Extrahepatic*** (ie, perihilar), and
- ***Distal extrahepatic***.

Perihilar tumors are the most common CCCs, and intrahepatic tumors are the least common. Perihilar tumors, also called Klatskin tumors (after ***Klatskin's*** description of them in ***1965***), occur at the bifurcation of right and left hepatic ducts ***(Clary et al; 2004)***.

Distal extrahepatic tumors are located from the upper border of the pancreas to the ampulla. More than 95% of these tumors are ductal adenocarcinomas; many patients present with unresectable or metastatic disease.

Pathophysiology:

Cholangiocarcinoma is a tumor that arises from the intrahepatic or extrahepatic biliary epithelium. More than 90% are adenocarcinomas, and the remainder are squamous cell tumors.

The ***etiology*** of most bile duct cancers remains undetermined. Long-standing inflammation, as with primary sclerosing cholangitis (PSC) or chronic parasitic infection, has been suggested to play a role by inducing hyperplasia, cellular proliferation, and, ultimately, malignant transformation. Intrahepatic cholangiocarcinoma may be associated with chronic ulcerative colitis and chronic cholecystitis.

Cholangiocarcinomas tend to grow slowly and to infiltrate the walls of the ducts, dissecting along tissue planes. Local extension occurs into the liver, porta hepatis, and regional lymph nodes of the celiac and pancreaticoduodenal chains. Life-threatening infection (cholangitis) may occur that requires immediate antibiotic intervention and aggressive biliary drainage.

Clinical History:

Symptoms include jaundice, clay-colored stools, bilirubinuria (dark urine), pruritus, weight loss, and abdominal pain.

- Jaundice is the most common manifestation of bile duct cancer. The obstruction and subsequent cholestasis tend to occur early if the tumor is located in the common bile duct or common hepatic duct. Jaundice often occurs later in perihilar or intrahepatic tumors and is often a marker of advanced disease. The excess of conjugated bilirubin is associated with bilirubinuria and acholic stools.
- Pruritus usually is preceded by jaundice, but itching may be the initial symptom of cholangiocarcinoma. Pruritus may be related to circulating bile acids.
- Weight loss is a variable finding and may be present in one third of patients at the time of diagnosis.
- Abdominal pain is relatively common in advanced disease and often is described as a dull ache in the right upper quadrant.

Physical:

- If the cholangiocarcinoma is located distal to the cystic duct takeoff, the patient may have a palpable gallbladder, which commonly is known as Courvoisier sign.
- An abdominal mass or palpable lymphadenopathy is uncommon, but hepatomegaly may be noted in as many as 25% of patients.

Causes:

The etiology of most bile duct cancers remains undetermined. Currently, gallstones are not believed to increase the risk of cholangiocarcinoma. Chronic viral hepatitis and cirrhosis also do not appear to be risk factors.

1. Infections :

- **a.** In Southeast Asia, chronic infections with liver flukes, *Clonorchis sinensis,* and *Opisthorchis viverrini* have been causally related to cholangiocarcinoma.
- **b.** Other parasites, such as *Ascaris lumbricoides,* have been implicated in the pathogenesis of cholangiocarcinoma.
- **c.** Observations have raised the possibility that bacterial infections with *Helicobacter* species may play an etiologic role in biliary cancer ***(Schottenfeld et al; 2006).***

2. Inflammatory bowel disease :

- **a.** A strong relationship exists between cholangiocarcinoma and primary sclerosing cholangitis. Cholangiocarcinoma generally develops in patients with long-standing ulcerative colitis and primary sclerosing cholangitis ***(Chalasani et al; 2000).***
- **b.** The lifetime risk of developing this cancer in the setting of primary sclerosing cholangitis is 10-20%. At increased risk are patients with ulcerative colitis without symptomatic primary sclerosing cholangitis and a small subset of patients with Crohn disease.

3. Chemical exposures :

- **a.** Certain chemical exposures have been implicated in the development of bile duct cancers, primarily in workers in the aircraft, rubber, and wood-finishing industries.

4. Cholangiocarcinoma occasionally has developed years after

administration of the radiopaque medium thorium dioxide.

5. **Congenital diseases of the biliary tree**, including choledochal cysts and Caroli disease, have been associated with cholangiocarcinoma.
6. **Other conditions** rarely associated with cholangiocarcinoma include bile duct adenomas, biliary papillomatosis, and alpha $_1$ -antitrypsin deficiency.

III) Peripheral T-Cell Lymphoma Arising in the Liver

Secondary liver involvement is common in patients with non-Hodgkin lymphoma (NHL), detected in up to 50% of patients who undergo pathologic staging ***(Lotz et al; 1976&Ferguson et al; 1973).***

In contrast, NHL arising in the liver is uncommon, and most cases are diffuse large B-cell lymphomas that manifest as space-occupying lesions. Low-grade B-cell lymphomas of mucosa-associated lymphoid tissue arising in the liver also have been reported and may transform to diffuse large B-cell lymphoma in some cases ***(Isaacson et al; 1995&Ye MQ et al; 2000&Avlonitis et al; 1999).***

By contrast, peripheral T-cell lymphoma (PTCL) arising in the liver is rare. Although patients with PTCL who sought care because of hepatic symptoms are described, many of these patients had systemic disease at the time of diagnosis, shown by tissue biopsy, bone marrow aspiration and biopsy,or radiologic studies ***(Lei KIK. 1988 &Andreola et al. 1988&Schweiger F. 2000).***

Although some of these NHLs may have arisen in the liver and subsequently disseminated, it is likely that most of these tumors were systemic and secondarily involved the liver.

B) BENIGN TUMOURS:

♦ Benign focal solid lesions of the liver

I. Cavernous Hemangioma, Liver:

Cavernous hemangioma is the most common primary liver tumor; its occurrence in the general population ranges from 0.4-20%, as reported by Karhunen in an autopsy series ***(Karhunen PJ. 1986).***

Cavernous hemangiomas arise from the endothelial cells that line the blood vessels and consist of multiple, large vascular channels lined by a single layer of endothelial cells and supported by collagenous walls. These tumors are frequently asymptomatic and incidentally discovered at imaging, surgery, or autopsy. Hemangiomas are uncommon in cirrhotic livers; the fibrotic process in cirrhotic liver may prohibit their development ***(Dodd et al; 1999).***

Usually, cavernous hemangiomas occur as solitary lesions; however, they may be multiple in as many as 50% of patients ***(Mergo et al; 1998).*** No lobar predilection exists, and the tumors may be associated with focal nodular hyperplasia ***(Vilgrain et al; 2000).*** Hemangiomas typically measure less than 5 cm; those larger than 4-5 cm are sometimes called giant hemangiomas ***(Yang et al; 2001&Cappellani et al; 2000).***

Pathophysiology:

The natural history of liver hemangioma is not completely understood. Hemangiomas are probably congenital in origin, and hereditary factors may play a role in the pathogenesis of some familial forms of these tumors. Although the growth of hemangiomas is reported in the literature, ectasia is believed to contribute to lesion enlargement ***(Nghiem et al; 1997).***

Moreover, according to the findings in a study by ***Brancatelli et al***, hemangiomas may become fibrotic and shrink in patients with progressive cirrhosis, leading to more difficulty with radiologic and pathologic diagnoses ***(Brancatelli et al; 2001).***

Sex:

A distinct female preponderance has been reported in surgical series, with a female-to-male ratio ranging from 5:1 to 6:1. However, in children and in autopsy series, cavernous hemangioma of the liver affects males and females equally .

Age:

Hemangiomas can occur in individuals of any age. The tumors frequently occur in middle-aged women.

Presentation:

The vast majority of hemangiomas (as many as 85%) are asymptomatic; however, hemangiomas may cause symptoms because of the compression of adjacent structures, rupture, acute thrombosis, or consumptive coagulopathy (i.e, *Kasabach-Merritt syndrome*).

Pressure on the stomach and duodenum caused by large pedunculated hemangioma lesions may cause vague abdominal pain, early satiety, nausea, and vomiting. Pedunculated hemangiomas may twist and cause acute abdominal pain ***(Tran-Minh et al; 1991).***

Compression of the inferior vena cava may result in Budd-Chiari syndrome ***(Hanazaki et al; 2001).***

Acute thrombosis may result in acute inflammatory changes that cause fever, abdominal pain, and abnormal results in liver function tests ***(Pol B et al; 1998).***

Spontaneous or posttraumatic rupture is a catastrophic complication that occurs in about 1-4% of hemangiomas; this condition has a considerable mortality rate, as high as 60% ***(Cappellani et al; 2000).***

Preferred Examination:

Most patients with liver hemangioma are asymptomatic. Clinical findings usually do not contribute to the diagnosis.

Laboratory test results may suggest anemia, and reduced hematocrit levels may be present in patients who have ruptured hemangiomas.

In patients who have giant hemangiomas that are associated with *Kasabach-Merritt syndrome*, bleeding and clotting laboratory parameters may be abnormal.

Most hemangiomas are incidentally detected on imaging studies. Ultrasonography is a cost-effective imaging modality for the diagnosis of a hemangioma. However, computed tomography (CT) scanning and/or MRI may be required to specifically diagnose a hemangioma.

Radiological findings:

I) Findings in Ultrasonography:

At ultrasonography, hemangiomas appear as well-circumscribed, uniformly hyperechoic lesions. The increased echogenicity has been postulated to be caused by multiple interfaces between the walls of the cavernous spaces and the blood within them ***(McArdle CR. 1978).***

In large hemangiomas, heterogeneous areas are interspersed within the hyperechoic mass. Atypical features include hypoechoic lesions with a thin hyperechoic rim or a thick rind and scalloped borders ***(Vilgrain et***

al; 2000). Note that hemangiomas may appear hypoechoic in fatty livers ***(Marsh et al; 1989).***

Color power or duplex Doppler ultrasound examinations have a limited role in the specific diagnosis of hemangioma ***(Perkins et al; 2000).*** Occasionally, a kilohertz shift in the low to mid range may be observed in the peripheral and central blood vessels in the hemangiomas.

II) Findings in Computed Tomography:

Hemangiomas are enhancing lesions that have characteristic dynamic features after the administration of contrast material. On nonenhanced CT scans, hemangiomas appear hypoattenuating relative to the adjacent liver. Calcification is uncommon; it may be marginal or central, spotty or chunky ***(Mitsudo et al; 1995).***

During the arterial-dominant phase, small hemangiomas show intense and uniform contrast enhancement and retain their contrast enhancement during the portal venous phase ***(Vilgrain et al; 2000).***

Wedge-shaped subcapsular or segmental perilesional enhancement may be noted adjacent to high-flow hemangiomas. These findings are possibly due to hemodynamic alterations in the liver ***(Jeong et al; 2000).***

The pattern of a peripheral, discontinuous, intense nodular enhancement during the arterial-dominant phase with progressive centripetal fill-in on CT scans is considered pathognomonic for hemangiomas. Pathologically, the nodular areas consist of small vascular spaces that are more densely packed than the rest of the lesion.

Atypical features of hemangiomas include the presence of arterioportal shunts and capsular retraction***(Yang et al; 2001***&***Shimada et al;1994).*** Rarely, a centrifugal pattern of contrast enhancement is seen ***(Kim et al; 2000).***

Degree of Confidence:

A globular enhancement pattern on CT scans (analogous to contrast-agent puddling on angiograms) is considered a highly sensitive (88%) and specific (84-100%) feature of hemangiomas ***(Leslie et al;1995&Quinn et al; 1992).***

III) Findings in Magnetic Resonance Imaging:

MRI is more sensitive and specific than other imaging modalities in the diagnosis of hemangiomas. Hemangiomas appear as smooth, lobulated, homogeneous, sometimes septated, hypointense lesions on T1-weighted images. On T2-weighted images, they appear hyperintense relative to the liver (ie, more pronounced on fast spin-echo images), and they remain as bright as cerebrospinal fluid or bile with increased echo time (TE) ***(McFarland et al; 1994).***

Rarely, the imaging features of heavily fibrotic (hyalinized) hemangiomas can be mistaken for those of metastases ***(Cheng et al; 1995).*** With the injection of contrast material (gadolinium chelates), lesions typically demonstrate peripheral nodular enhancement with progressive, centripetal fill-in that usually appears after 5-30 minutes.

Large hemangiomas may appear cystic on images as a result of recurrent hemorrhage or myxomatous degeneration. In some hemangiomas, MRI may demonstrate fluid-fluid levels due to the sedimentation of blood products. The supernatant layer consists of unclotted serous blood, and the sediment consists of red blood cells. Definitive diagnosis is often difficult ***(Soyer et al; 1998).***

Degree of Confidence:

MRI is more sensitive and specific than other imaging modalities in the diagnosis of hemangiomas. On the basis of liver hemangioma

characteristics on T2-weighted images (both morphologic and quantitative T2 values), MRI has a sensitivity of 100%, a specificity of 92%, and an accuracy rate of 97%.

Hemangiomas that show early, homogeneous contrast enhancement on dynamic CT scans and/or MRI may be mistaken for other hypervascular liver tumors such as hepatoma, focal nodular hyperplasia, adenoma, and hypervascular metastases.

The absence of a history of cirrhosis and/or primary malignancy is an important factor in diagnosing hemangioma. The characteristic features of a hemangioma on dynamic CT scans, red blood cell scintigraphy, and/or MRI permit confident diagnosis in more than 95% of cases.

IV) Findings in* Nuclear Imaging*:

Red blood cell-tagged technetium-99m (^{99m} Tc) scintigraphy with single photon emission CT (SPECT) scanning permits a specific diagnosis of hemangiomas ***(El-Desouki et al; 1999).***

The lesions characteristically show decreased activity on early dynamic images and delayed filling from the periphery of the lesion.

Degree of Confidence:

The reported sensitivity is 97%, specificity 83%, and accuracy 96% for red blood cell-tagged ^{99m} Tc scintigraphy in the diagnosis of hemangiomas.

V) Findings in* Angiography*:

At angiography, the feeding vessels of the hemangioma are of normal caliber, except those in the large tumors. During the late arterial/hepatic parenchymal phases, a dense, nodular pattern of

opacification of the dilated vascular spaces persists into the venous phase ***(Kadir S; 1986).***

Degree of Confidence

Although hemangiomas have characteristic angiographic features, the use of angiography is not warranted in the diagnosis of hemangioma, given the diagnostic capabilities of less invasive techniques, such as helical CT scanning and MRI.

Differential Diagnoses:

- Focal Nodular Hyperplasia.
- Hepatocellular Carcinoma.
- Liver Metastases.

Other Problems to Be Considered

- Hepatoma.
- Adenoma.
- Hypervascular metastases.

Treatment:

Most hemangiomas are asymptomatic and treated conservatively with watchful expectancy. Absolute indications for surgery include rupture, a rapid change in size, and the presence of Kasabach-Merritt syndrome ***(Hochwald et al;2000&Gedaly et al;1999).***

Large symptomatic hemangiomas are a relative indication for surgery. *Surgical enucleation* with blunt dissection is the preferred surgical technique. In symptomatic patients who are poor surgical candidates, *transcatheter embolization* is an attractive alternative (***Cappellani et al;2000&Kadir S;1986).***

Imaging:

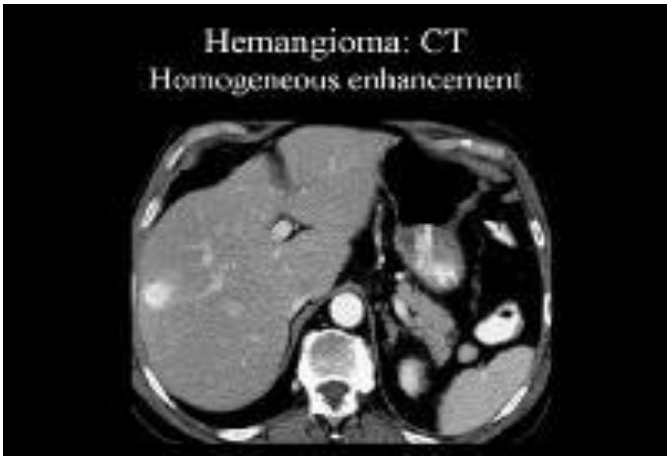


***Fig. 5*: Contrast-enhanced computed tomography (CT) scan that was obtained during the arterial-dominant phase. This image demonstrates a hemangioma with homogeneous and intense contrast enhancement.**

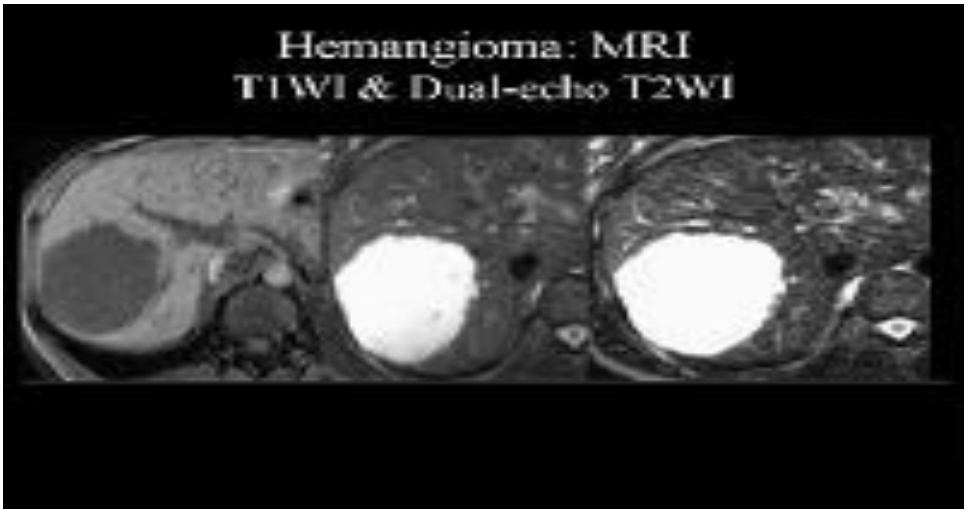


***Fig. 6:* Magnetic resonance image (MRI) of a hemangioma. The lesion appears as a hypointense mass on T1-weighted MRIs (T1WI) and as a hyperintense mass on dual-echo T2-weighted MRIs (T2WI). Note that the signal intensity of the lesion is similar to that of the adjacent cerebrospinal fluid.**

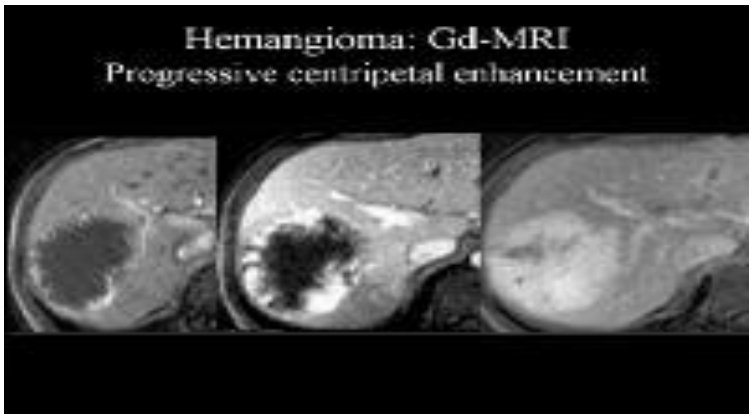


***Fig. 7*: Dynamic gadolinium (Gd)-enhanced magnetic resonance images (MRIs). These images demonstrate the progressive, centripetal contrast enhancement in a hemangioma.**

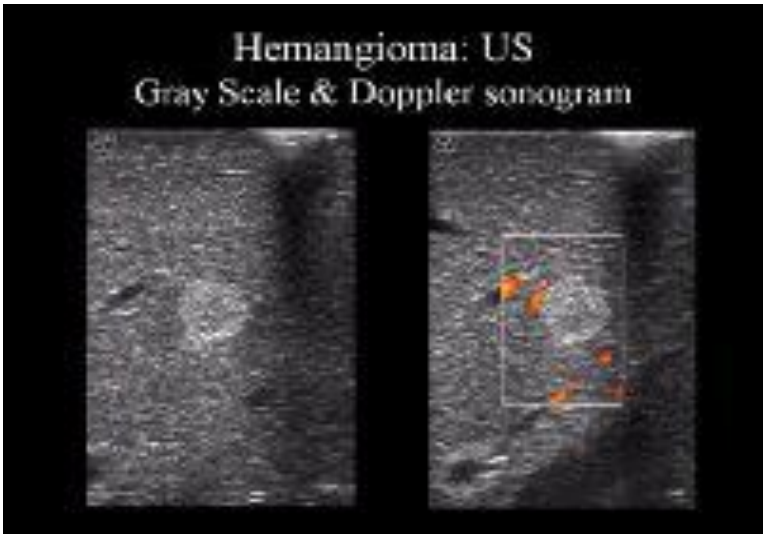


***Fig. 8*: Gray-scale and Doppler ultrasonographic (US) images. These sonograms show a well-defined, uniformly hyperechoic liver mass with peripheral feeder vessels that are characteristic of a hemangioma.**

II. Focal Nodular Hyperplasia:

Focal nodular hyperplasia (FNH) is the second most common tumor of the liver, surpassed in prevalence only by hepatic hemangioma ***(Craig et al; 1980).***

FNH is believed to occur as a result of a localized hepatocyte response to an underlying congenital arteriovenous malformation.

FNH is a hyperplastic process in which all the normal constituents of the liver are present but in an abnormally organized pattern. Results of liver function tests in these patients usually are within the reference range.

The use of contraceptive agents has not been implicated in the pathogenesis of FNH, but their use is associated with an increased rate of complications in patients with FNH, and they may be a factor in the development of FNH.

In symptomatic females, hemorrhagic foci or infarctions may occur within the FNH; these are aggravated by administration of contraceptive agents. The rare complication of a spontaneous rupture into the peritoneum has also been associated with contraceptive use.

In most patients, the clinical course is silent, and FNH is incidentally discovered during cross-sectional imaging, angiography, radionuclide liver scanning, or surgery.

Most cases of FNH occur as a solitary lesion (80-95%), but multiple lesions may occur ***(Wanless et al; 1989).***

Malignant transformation of FNH has not been reported. FNH must be differentiated from a fibrolamellar variant of hepatocellular carcinoma, with which it shares imaging and gross features.

Pathophysiology:

FNH is not a true neoplasm, but it probably represents a local hyperplastic response of hepatocytes to a congenital vascular anomaly ***(Wanless et al; 1985).*** It is a proliferation of normal, nonneoplastic hepatocytes that are abnormally arranged. Supporting this hypothesis is the fact that FNH is found in association with cavernous hemangiomas, as well as other vascular malformations of other organs and neoplasms of the brain ***(Wanless. 1990&Ndimbie et al;1990&Rhodes et al;1978).***

Intermediate lesions (ie, lesions with characteristics of both cavernous hemangiomas and FNH) have been reported ***(Ndimbie et al;1990).*** A rare transitional lesion that has been reported as a mixed hamartoma and found most often in infants and children has similarities to both FNH and hemangioma ***(Craig et al; 1980&Saul SH. 1994).***

It is hypothesized that a congenital vascular malformation (either an arteriovenous shunt or localized hyperperfusion) triggers focal hepatocellular hyperplasia.

On pathologic examination, anomalous arterial branches, unaccompanied by portal venous branches, have been seen feeding the numerous small lobules that constitute the FNH lesion ***(Wanless et al; 1985).*** As with hyperplasia and hypertrophy seen around vascular malformations in the extremities, hepatic hyperplasia is seen in the liver.

FNH is a localized, well-delineated focal lesion, not a diffuse mass, within an otherwise normal liver. In 80-90% of patients, the FNH lesion is solitary, and the macroscopic appearance is a highly characteristic finding. While FNH has no capsule, it tends to be a fairly well marginated, lobulated, subcapsular mass.

On naked-eye examination of a gross pathologic specimen, the lesion is often lighter than the surrounding liver tissue. In some patients, FNH blends in with normal liver tissue, so that distinguishing surrounding normal liver tissue from FNH may be difficult if a gross pathologic specimen is used.

on a cut specimen; the lesion appears as a central stellate scar with radiating fibrous septa dividing the tumor into lobules. The central scar contains an arterial malformation with spiderlike branches supplying the component nodules.

Results of microscopic examination confirm that the central stellate scar is associated with radiating fibrous septa dividing the hyperplastic nodules into smaller units. The tumor is composed of multiple spherical aggregates of hepatocytes, which often contain increased amounts of fat (triglycerides) and glycogen. Proliferation of the biliary structures is marked, and they are surrounded by inflammatory cells, primarily at the periphery of the fibrous septa.

Bile duct proliferation shows no connection to the biliary tree. Arteries in the fibrous septa have thick walls; this change is associated with intimal and medial fibromuscular hyperplasia of the larger arteries. *Sinusoidal* dilatation and, occasionally, hemorrhagic foci and areas of infarction are seen. *Kupffer cells* are usually present in the lesion; in fact, the lesions may have a concentration of them higher than that of normal liver tissue.

Frequency:

FNH is the second most common benign hepatic tumor (after hemangioma), constituting about 8% of primary hepatic tumors in an autopsy series ***(Craig et al; 1980)***.

Mortality/Morbidity:

Mortality and morbidity are related to hepatic surgery; surgery is occasionally performed in patients who are symptomatic or in patients in whom imaging findings are equivocal. The natural morbidity resulting from the lesions is low, and no deaths due to FNH have been reported, at least to our knowledge.

Sex:

FNH is found most commonly in women (80-95% of cases) in their third and fourth decades of life.

Age:

FNH is found most commonly in the third and fourth decades of life. However, cases can be seen in childhood or late adulthood.

Presentation:

In 50-80% of cases, FNH is detected as an incidental finding at autopsy, by laparotomy,or during radiologic investigation ***(Saul SH. 1994&Klatskin G.1977&Knowles et al;1978).***

Symptomatic patients most often complain of an abdominal mass (10-15% of all patients) or abdominal pain ***(Saul SH.1994&Klatskin G.1977&Knowles et al;1978).*** The pain is usually caused by larger lesions, which stretch the liver capsule or have a mass effect on adjacent organs. Results of liver function tests are usually normal.

Patients using oral contraceptives are more likely to present with symptoms, because contraceptive use is often linked to tumor hemorrhage or infarction. The relationship between FNH and the use of oral contraceptives, however, is often misunderstood, in that FNH itself is not caused or even associated with the use of oral contraceptives***(Knowles et al;1978&Ishak KG.1979&Kerlin et al;1983).***

We believe that this misconception most likely arose because hepatocellular adenoma, a neoplasm that has been definitively related to the use of oral contraceptives, was mistakenly included in early series of FNH. On the other hand, however, oral contraceptives may promote the growth of FNH ***(Craig et al; 1980)&(Ishak KG.1979)***

Classification:

Currently, FNH is subdivided into 2 types:

I. Classic (80%).

II. Nonclassic(20%) ***(Nguyen et al; 1999).***

I. Nonclassic FNH is further divided into 3 subtypes*:*

1. Telangiectatic FNH,
2. FNH with cytologic atypia,
3. Mixed hyperplastic and adenomatous FNH.

II. Classic FNH contains all of the 3 characteristics:

1. Abnormal nodular architecture,
2. Malformed vessels, and
3. Cholangiolar proliferation.

Nonclassic FNH contains 2 of the 3 components but always includes bile duct proliferation ***(Nguyen et al; 1999).***

Because telangiectatic FNH shares several morphologic patterns with hepatocellular adenomas, ***Paradis et al*** conducted a study in which they attempted to reclassify telangiectatic FNH by molecular analysis ***(Paradis et al; 2004).*** Their results showed that telangiectatic FNH has a molecular pattern closer to that of hepatocellular adenomas than to FNH and suggest that telangiectatic FNH instead be referred to as *"telangiectatic hepatocellular adenomas."*

Differential Diagnoses:

- Cavernous hemangioma.
- Liver cholangiocarcinoma.
- Hepatic adenoma.
- Hepatocellular carcinoma.
- Metastases.

Radiological Findings:

Although FNH usually has no clinical significance, recognition of the radiologic characteristics of FNH is important to avoid unnecessary surgery, biopsy, and follow-up imaging.

I) Plain radiographs have little to offer in the diagnosis of FNH. Radiographs may demonstrate other causes of abdominal pain in symptomatic patients, including gallstones, nonspecific hepatomegaly, and other soft-tissue masses. The presence of calcification in a liver lesion suggests a diagnosis other than FNH because only 1% of patients with FNH have calcification ***(Dähnert W. 2006).***

Degree of Confidence:

Plain radiography has low specificity and sensitivity in the diagnosis of FNH.

II) Findings in Ultrasonography: The US findings of FNH are variable. The lesion may appear as a homogeneous mass that is isoechoic, hypoechoic, or hyperechoic. FNH has a mass effect that may displace intrahepatic blood vessels. Only 18% of patients have a central scar.

Doppler sonograms demonstrate an enlarged afferent blood vessel with central arterial hypervascularity and centrifugal filling to the periphery in a spokelike manner. Large draining veins may be seen at the

periphery of the mass. High-velocity Doppler signals with arterial pulsatility may be recorded from arteriovenous shunts.

Echo-enhanced Doppler US has a high sensitivity for detection of the feeding artery and for depiction of the radial vascular architecture in FNH, especially for lesions that are located in the liver's left lobe.

Power Doppler US has increased sensitivity for FNH and may help distinguish it from hepatocellular carcinoma. The use of dynamic contrast-enhanced US is increasingly being used to diagnose FNH.

Ungermann et al used dynamic contrast-enhanced US to study the presence of a spoke-wheel pattern and the typical symptoms of FNH, in relation to lesion size, in 28 patients ***(Ungermann et al; 2007).***

According to the investigators, contrast-enhanced US can be the final diagnostic method for lesions that are larger than 3 cm and have a typical spoke-wheel structure on contrast-enhanced US. They concluded, however, that if the spoke-wheel pattern is not present and if there is no central scar, the diagnosis of FNH cannot be made specifically by contrast enhanced US alone ***(Ungermann et al; 2007).***

Attal et al described the features of US, CT, and MRI regarding telangiectatic FNH, and they compared the findings with histopathologic findings in 13 cases of FNH. ***(Attal et al; 2003).*** The results of the study showed that telangiectatic FNH differs from typical FNH on images: the atypical features that were often observed with telangiectatic FNH were the lack of a central scar, heterogeneous lesions, hyperintensity on T1-weighted MRI, strong hyperintensity on T2-weighted MRI, and persistent contrast enhancement on delayed contrast-enhanced CT or T1-weighted MRI ***(Attal et al;2003).***

Degree of Confidence:

The FNH lesion may be difficult to detect, because it is often hypoechoic to normal liver tissue. US specificity is low, but the specificity can be increased with Doppler US and echo enhancement. As is the case with other cross-sectional imaging, however, a specific diagnosis is sometimes not possible because the FNH lesion is similar to lesions of other benign and malignant diseases.

False Positives/Negatives:

The lesion may be missed entirely if the signal is isoechoic. US findings of FNH overlap with those of hepatic adenomas and hepatocellular carcinomas, although the use of Doppler US, particularly power Doppler and echo-enhanced Doppler US, improves the sensitivity and specificity.

III) Findings in Computed Tomography: On nonenhanced CT scans, FNH may appear as an isoattenuating or slightly hypoattenuating mass. Nonenhanced images are important because FNH may be missed without a precontrast study. For the optimal evaluation of FNH, a helical CT scan with a 4-phase study should be performed. This evaluation should include nonenhanced and hepatic arterial, portal venous, and delayed–phase examinations ***(Carlson et al;2000).***

After the administration of contrast material, the lesion becomes *hyperattenuating* relative to the surrounding liver in the *arterial phase*; this occurs approximately 20-30 seconds after the bolus of contrast agent is administered. In the *portal venous phase*, 70-90 seconds after the bolus injection, FNH is less conspicuous and becomes *isoattenuating* to the rest of the liver. During the delayed phase, approximately 5-10 minutes after the bolus injection, FNH is isoattenuating with normal liver.

In 15-33% of patients, conventional CT scans show the hypoattenuating stellate central scar with a central core and radiating fibrous septa. The central scar may become hyperattenuating on delayed images because of delayed contrast washout from the scar; however, the central scar does not go through a hypoattenuating phase on helical CT scans. The scar is demonstrated as a hyperattenuating region in the portal venous phase. The central artery traversing the central scar may show early enhancement in the arterial phase.

Degree of Confidence:

When characteristic features are seen in the appropriate clinical setting, a fairly confident diagnosis can be made. Unfortunately, CT features of other benign and malignant lesions can mimic those of FNH. Because of the nature and pathogenesis of FNH, it is difficult to obtain an accurate diagnosis of FNH on the basis of the clinical presentation and radiographic studies.

False Positives/Negatives:

Although triple-phase CT scanning accurately characterizes most FNH lesions, CT findings are not as definitive in some patients with FNH. Rarely, a false-positive diagnosis of FNH may occur with fibrolamellar hepatocellular carcinoma as well as other well-differentiated variants of hepatocellular carcinoma.

IV) Findings in Magnetic Resonance Imaging: FNH usually displays a homogeneous signal intensity on MRIs. In 94-100% of FNH patients, the FNH lesion is isointense to hypointense on T1-weighted images; in 6%, the signal intensity on T1-weighted images may be hyperintense; and on T2-weighted images, the lesion is slightly hyperintense to isointense in 94-100% of patients. The central scar of FNH is hypointense on T1-weighted images, but on T2-weighted images, the central

scar shows a variable signal-intensity pattern. On T2-weighted images, the scar appears hyperintense in 75% of patients and hypointense in 25% of patients ***(Dähnert W. 2006).***

After the administration of a gadolinium-based contrast agent, the enhancement pattern parallels that of contrast-enhanced CT. Dense enhancement is seen in the arterial phase, and the lesion becomes isointense during the portal venous phase and isointense on delayed images. Late and prolonged enhancement of the central stellate scar occasionally occurs.

MRI findings are not pathognomonic for FNH, but the use of MRI reticuloendothelial agents, such as superparamagnetic iron oxide (SPIO) and ultrasmall superparamagnetic iron oxide (USPIO), increase the specificity. On SPIO-enhanced T2-weighted images, FNH shows decreased signal intensity because of iron uptake by Kupffer cells. This finding is not specific to FNH, because hepatocellular adenoma and hepatocellular carcinoma also may contain Kupffer cells.

Degree of Confidence:

The MRI findings in patients who have FNH are not pathognomonic for the disease. However, the use of MRI reticuloendothelial agents, such as USPIO and SPIO, can increase MRI's specificity. In the diagnosis of FNH, MRI has a sensitivity of 70% and a specificity of 98% ***(Dähnert W. 2006).***

False Positives/Negatives:

A false-positive diagnosis of FNH may occur with fibrolamellar hepatocellular carcinoma and other well-differentiated forms of hepatocellular carcinoma. On SPIO-enhanced T2-weighted images, hepatocellular adenoma and hepatocellular carcinoma can also show decreased signal intensity, because Kupffer cells may be present.

V) Findings in Nuclear Imaging: The best imaging modalities for characterizing FNH are those modalities that can delineate the lesion's central scar or can show Kupffer cell activity. The best modalities for identifying the central scar are CT and MRI, and Kupffer cell activity is best demonstrated by radionuclide scans. In the future, however, MRI superparamagnetic contrast agents may challenge radionuclide scanning.

Detection of Kupffer cells in FNH has historically been achieved using technetium-99m (^{99m}**Tc**) sulfur colloid scanning. In 60-70% of FNH patients, these scans show normal or increased uptake of ^{99m}**Tc** sulfur colloid. In 30-40% of patients, Kupffer cells are not sufficiently concentrated in the FNH lesion; the lesion may even be photon deficient ***(Dähnert W. 2006).***

The uptake of ^{99m}**Tc** – hepatoiminodiacetic acid (HIDA) may be normal to increased in 40-70% of patients, but the lesion may be photon deficient in as many as 60% of patients. With ^{99m}Tc-tagged RBCs, uptake is increased during the early phase, followed by decreased uptake ***(Dähnert W. 2006).***

Degree of Confidence:

^{99m}**Tc** sulfur colloid uptake in patients with FNH depends on the concentration of Kupffer cells in the FNH lesion. Unfortunately, other hepatocellular neoplasms, such as a hepatocellular adenoma and hepatocellular carcinoma, can also have Kupffer cells and demonstrate ^{99m}Tc sulfur colloid uptake.

False Positives/Negatives:

Hepatic adenoma, hemangioma, hepatoblastoma, liver herniation, and hepatocellular carcinoma can give rise to similar appearances on ^{99m}**Tc** sulfur colloid scans.

VI) Angiography Findings: Angiographic findings demonstrate a discretely marginated mass. When the mass is small, the arteries supplying the mass break up into small branches, which appear to permeate the FNH and form a reticular pattern. These branches are not dilated, but the overall impression is that of increased vascularity. Vascularity may be decreased within the central stellate scar. In the parenchymal phase, a fine, homogeneous granularity is demonstrated, with an occasional lucent ring around the mass.

In large tumors, the dilated main feeding artery perforates the center of the tumor. Peripheral arteries arise from the central artery, arranged in a spoke-wheel pattern.

Degree of Confidence:

Although the typical angiographic findings are present in only 33% of patients, the diagnosis of FNH may still be suggested ***(Dähnert W. 2006).*** FNH may instead appear similar to an adenoma.

False Positives/Negatives:

Only 33% of patients have the characteristic findings of FNH; therefore, lesions may be missed, or an incorrect diagnosis, such as a hepatocellular adenoma, may be derived in up to 67% of patients ***(Dähnert W. 2006).***

Intervention:

Surgery is occasionally performed in patients who are symptomatic or in patients in whom imaging findings are equivocal.

Shen et al explored the diagnosis and treatment of FNH by studying 86 patients with a diagnosis of FNH that was confirmed pathologically between 1999 and 2006 ***(Shen et al; 2007).***

In 80 of the patients, there was a solitary focus; and in 6 patients, there were multiple foci. In 69 patients, the diameter of the tumor was less than 5 cm; in 15 patients, the tumor diameter was 5-10 cm; and in 2 patients, the diameter of the tumor was greater than 10 cm ***(Shen et al; 2007).*** Overall, a correct preoperative diagnosis was made in 59.3% of patients (51/86). Doppler color flow imaging provided a correct preoperative diagnosis in 32.9%, CT in 60.3%, and MRI in 77.4%.

All of the patients underwent tumor resection, and all displayed good curative results ***(Shen et al; 2007).***

The investigators concluded that CT and MRI are both important methods for diagnosing FNH but that it is difficult to make a definitive preoperative diagnosis for partial classic and for all nonclassic cases of FNH. As a result of their findings, *Shen et al* suggested that patients undergo tumor resection if they have clinical symptoms or have an indefinite diagnosis ***(Shen et al; 2007).***

Imaging:

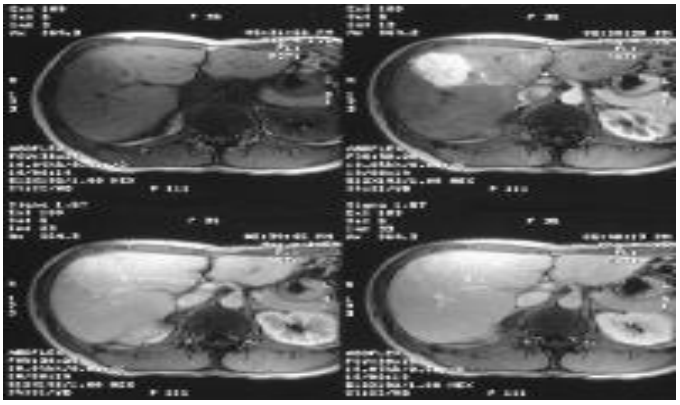


***Fig. 9*: Dynamic MRIs in a 36-year-old woman referred for a gallbladder sonography, during which the patient was found to have a vague ill-defined hypoechoic mass in the right lobe of the liver (not shown). (Top left) Gadolinium-enhanced T1-weighted MRI demonstrates an ill-defined low-signal-intensity mass. (Top right) The mass enhances intensely in the arterial phase after the administration of contrast medium. (Bottom left) Minor enhancement persists in the portal venous phase. (Bottom right) The lesion becomes isointense relative to the liver on delayed images.**

a. **b.**

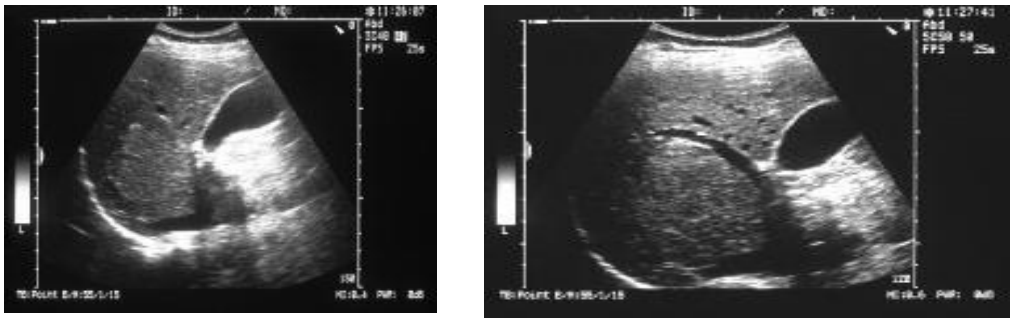


***Fig. 10*:**

a. Longitudinal sonogram through the liver and gallbladder in a 38-year-old woman referred for a gallbladder scanning. Image shows an ill-defined hyperechoic mass in the right lobe of the liver.

b. Longitudinal sonogram (more medial section than in Image 2) in a 38-year-old woman referred for a gallbladder scanning. Sonogram shows mass effect from the tumor, as demonstrated by the arching of the portal vein anteriorly.

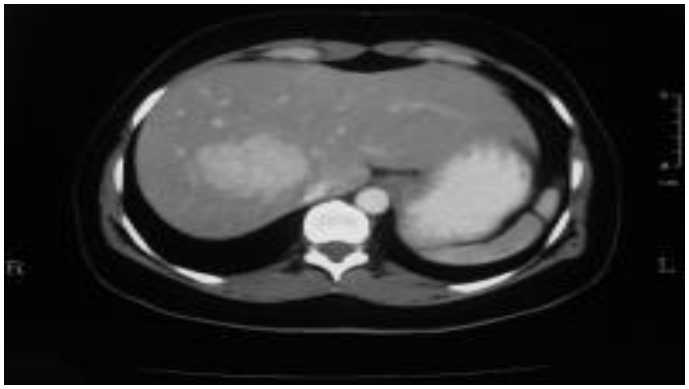


Fig. 11: **Enhanced axial CT scan through the liver in the arterial phase in a 38-year-old woman referred for gallbladder scanning. The mass demonstrates intense enhancement.**

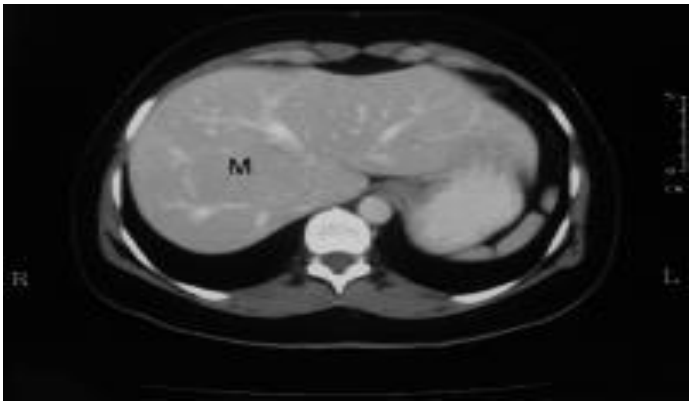


Fig. 12**: Delayed portal venous phase enhanced axial CT scan in a 38-year-old woman referred for gallbladder scan. Image shows stretching of the portal vein and the right hepatic vein around the mass (M).**

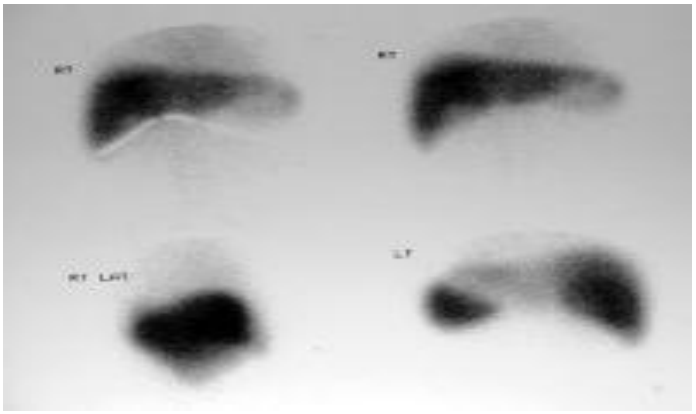


Fig. 13: ***Technetium-99m sulfur colloid scans in a 38-year-old woman referred for gallbladder scan.***

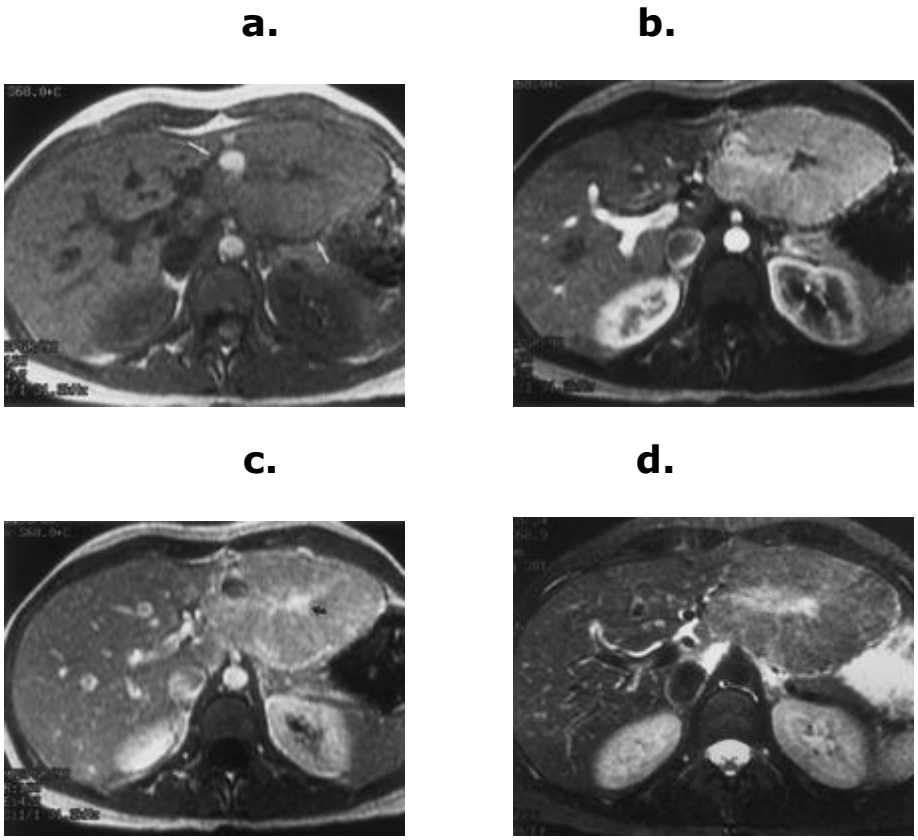


***Fig. 14*: Focal nodular hyperplasia in a 31-year-old woman who presented with abdominal pain.**

(a) T1-weighted spin-echo (spoiled gradient-echo) MR image of the liver shows a large, isointense mass (arrows) almost completely replacing the lateral segment of the left hepatic lobe.

(b) On a T1-weighted arterial-phase MR image obtained after intravenous bolus injection of gadopentetate dimeglumine, the lesion demonstrates homogeneous bright enhancement.

(c) T1-weighted 5-minute delayed-phase MR image shows enhancement of the central scar (arrow).

(d) On a T2-weighted MR image, the focal nodular hyperplasia shows mild hyperintensity relative to the background liver. The central scar appears hyperintense.

III. Hepatic adenoma

Hepatic adenoma is a rare, benign tumor of the liver ***(Micchelli et al; 2008& Ibrahim et al; 2007).*** Since the **1960s**, a dramatic increase in the incidence of the disease has occurred; this increase is attributed to the advent of oral contraceptive pills (OCPs).

Patients taking higher potency hormones, patients of advanced age, or patients with prolonged duration of use have a significantly increased risk of developing hepatocellular adenomas. Currently, decreases in dosages and the types of hormones contained in OCPs have led to a reduction in incidence ***(Klatskin G; 1977&Rooks et al; 1997).***

Two types of hepatic adenoma have been identified, including:

- **Adenomas of *bile duct origin*:** usually smaller than 1 cm and are not of clinical interest; typically, they are found incidentally on postmortem examinations.
- **Adenomas of *liver cell origin*:** larger on average, they measure 8-15 cm and are often clinically significant ***(Herman et al; 2000&Kume et al; 1997).***

Pathophysiology:

Histologically, sheets of well-differentiated hepatocytes characterize hepatic adenomas. The hepatocytes contain fat and glycogen and can produce bile; however, no bile ducts are present. A characteristic lack of portal vein tracts and terminal hepatic veins is noted. Most hepatic adenomas do not contain Kupffer cells.

Hepatocellular adenomas are tan in color, smooth, well circumscribed, fleshy in appearance, and vary from 1-30 cm in size. They have large blood vessels on the surface, and the lesions may outgrow their arterial blood supply, causing necrosis within the lesions.

A fibrous capsule may be present or absent; if absent, this may predispose to intrahepatic or extrahepatic hemorrhage.

Most hepatocellular adenomas present as solitary lesions in the lobe of the liver; however, tumors do occur in both the right lobe and the left lobe, and up to 20% of cases involve multiple lesions.

The pathogenesis is thought to be related to a generalized vascular ectasia that develops due to exposure of the vasculature of the liver to oral contraceptives and related synthetic steroids. Estrogen may exert an influence via estrogen receptors on hepatocytes. However, this remains controversial ***(Baum et al; 1973).***

Adenomas also have been associated with diabetes mellitus and glycogen storage disease (GSD), leading to speculation as to whether imbalances between insulin and glucagon also play a role. Patients with GSD are more likely to present with multiple lesions. Lesions associated with GSD often appear in younger patients (early third decade of life) and have a male-to-female ratio of 2:1.

In this group, the abnormal amounts of stored glycogen may have some effect, perhaps oncogene stimulation. Insulin and glucagon appear to play a larger role because GSD-related adenomas have been reported to seemingly disappear with dietary manipulation.

A distinct pathologic entity known as ***hepatic adenomatosis*** has been identified. Although overlap is possible, *adenomatosis* is generally defined as the presence of more than 10 adenomas within the liver in the absence of steroid use or by persistence after steroid withdrawal. Adenomatosis affects both men and women and is associated with elevations of alkaline phosphatase ***(Lee RG; 1994).***

Frequency:

Although hepatic adenomas may be idiopathic, the lesions are most often seen in young women who use oral contraceptives ***(Micchelli et al; 2008&Ault et al; 1996&Gyorffy et al; 1989).***

The incidence among long-term users of oral contraceptives is approximately 4 cases per 100,000 ***(Rooks et al; 1979).*** In women who do not use oral contraceptives or have used them for less than 2 years, the incidence is 1 case per million.

In addition, the incidence of hepatic adenomas is increased in patients with glycogen storage disease, diabetes mellitus, hemochromatosis, or acromegaly, galactosemia, beta-thalassemia, or tyrosinemia as well as in males using anabolic steroids ***(Reddy et al; 1993)***. Case reports by *Hill et al* indicated that hepatic adenoma is also an unusual complication of pregnancy ***(Hill et al; 1997).***

Mortality/Morbidity:

Hepatic adenomas may rupture and bleed (20%) causing right upper quadrant pain ***(Casillas et al; 2000&Welch et al; 1989)***; rarely, rupture may lead to hemorrhagic shock.

Although they are benign lesions, hepatic adenomas can undergo malignant transformation (13%) to hepatocellular carcinoma (HCC) ***(Micchelli et al; 2008&Gyorffy et al; 1989).*** *Malignant transformation* is rare, but for this reason, surgical resection is advocated in most patients with presumed hepatic adenomas ***(Ibrahim et al; 2007&Herman et al; 2000&Ault et al; 1996).***

Pregnancy has been associated with hepatic adenoma, and rupture of the adenoma during pregnancy has been associated with high rates of maternal and fetal mortality.

Race:

No known racial predilection for hepatic adenomas exists.

Sex:

In a retrospective analysis of 437 patients with liver tumors, 44 patients had hepatic adenoma ***(Weimann et al; 1997).*** Of these patients, a male-to-female ratio is 1: 3.9 (9 men and 35 women).

Age:

In the same study, the mean patient age was 34 years (15-64 y) in those affected by hepatic adenoma (44 patients) ***(Weimann et al; 1997).***

Presentation:

Although benign, hepatic adenomas can present a diagnostic challenge because the lesions can be difficult to distinguish from other benign or malignant hepatic tumors. Clinically, patients with hepatic adenoma may be asymptomatic, and lesions may be found incidentally during laparotomy or when radiologic studies are performed. Salient features of the history and physical examination may include the following:

a) History:

* Pain in the right upper quadrant or epigastric region is common, occurring in 25-50% of patients with hepatocellular adenomas.
* Lesions may be noticed by patients as a palpable mass. Lesions may also be discovered incidentally during an abdominal imaging study for an unrelated reason.
* History of birth control or anabolic steroid use should be elicited in patients with suspected hepatocellular adenomas ***(Gyorffy et al; 1989).***

* Patients may also present with severe, acute abdominal pain with bleeding into the abdomen, which results in signs of shock (e.g., hypotension, tachycardia, and diaphoresis).
* Hemoperitoneum occurs more frequently if the patient is taking a high-dose OCP, is actively menstruating or pregnant, or is within 6 weeks postpartum. Location of the lesion also is important, with those near the surface of the liver more prone to causing hemoperitoneum ***(Mortele et al; 2002).***

b) Physical examination:

The physical examination findings are often nonspecific. Patients may be asymptomatic, or they may appear ill, with pallor and abdominal distress. Palpable tender or non tender mass in the right hypochondrium.

c) Findings consistent with hemorrhage:

Vital signs: *Tachycardia *Hypotension *Orthostasis.

d) Head, ears, eyes, nose, and throat (HEENT) examination:

* Anicteric sclera (Jaundice has been reported due to compression of the biliary tree by the tumor.).
* Possible pale conjunctiva, if hemorrhage has occurred.
* Cardiovascular findings - Tachycardia if actively bleeding.

e) Abdominal findings:

* Possible right hypochondrial mass with or without tenderness.
* Possible fluid wave in cases of hemoperitoneum.
* Possible peritoneal signs, including guarding or rebound in cases of tumor rupture.

f) ***Skin findings***: Possible Grey-Turner sign or Cullen sign in cases of hemoperitoneum.

Differential Diagnoses:

- Cholangiocarcinoma.
- Colon Cancer,Adenocarcinoma.
- Hepatic Carcinoma,Primary.
- Malignant Melanoma.
- Metastatic Cancer, Unknown Primary Site.

Other Problems to Be Considered:

- Echinococcal cyst.
- Focal fatty change.
- Focal nodular hyperplasia.
- Hepatoblastoma.
- Inflammatory pseudotumor.
- Leiomyosarcoma.
- Lymphoma.
- Nodular regenerative hyperplasia.

Laboratory Studies:

- Serologically, hepatocellular adenomas are a diagnosis of exclusion. No specific serologic studies exist.
- Serum *aminotransferase* (aspartate aminotransferase [AST]/alanine aminotransferase [ALT]) levels are mildly elevated in approximately 50% of patients, due to the mass effect of the tumor.
- Serum *alpha-fetoprotein* (AFP) levels are within the reference range in patients with hepatocellular adenoma. Elevations are noted in 50% of HCC cases. Thus, finding an elevated AFP represents either a primary carcinoma or an adenoma that has undergone

malignant transformation. An AFP level within the reference range does not eliminate HCC from the differential diagnosis.

- Elevated *carcinoembryonic antigen* (CEA) levels suggest metastasis from the colon.
- Serologies for amoebiasis and echinococcus should be considered if the lesion appears cystic.

Preferred Examination:

A combination of multiphasic CT scans and gadolinium-enhanced MRI is best to identify most hepatic lesions. Certain characteristics, such as arterial enhancement and the presence of fat and hemorrhage, suggest that the lesion represents hepatic adenoma. If an enhancing central scar is seen, the diagnosis of FNH can be made. Nuclear medicine studies can also be helpful. Most hepatic adenomas do not demonstrate uptake on sulfur-colloid and gallium-67 (^{67} Ga) scans ***(Wojtowycz et al; 1995).***

Limitations of Techniques:

Although CT scanning, MRI, and nuclear medicine studies may help characterize lesions as adenomas, the findings are frequently nonspecific, and biopsy and/or resection may be necessary.

Radiological Findings:

Usually, plain radiographs of the abdomen provide no findings to suggest the diagnosis of hepatic adenoma. The liver is usually normal in size. Rarely, coarse calcifications may be seen in the right upper quadrant on radiographs, but this finding is nonspecific.

I) *Findings in* Ultrasonography:

On ultrasound, hepatic adenomas demonstrate variable echogenicity. The lesions may be hypoechoic, isoechoic, or hyperechoic

relative to liver parenchyma. Usually, differentiating hepatic adenomas from other liver lesions such as FNH or HCC is not possible based on either gray scale or Doppler ultrasonographic characteristics.

The primary role of ultrasound is to screen patients with hepatic masses that are discovered incidentally or who have a clinical history of abnormal liver function test results. Further imaging is then indicated using MRI, CT scanning, and/or nuclear medicine.

Morin et al, however, report that ultrasound can be used with specific contrast media and specialized imaging techniques to fully characterize the enhancement pattern of hepatic lesions, which, the authors indicate, are similar to that achieved with contrast-enhanced, multiphasic CT scanning and MRI ***(Morin et al; 2007).***

II)*Findings in* Computed Tomography:

Hepatic adenomas are often discovered incidentally on CT scans that are performed for other reasons. Once identified, a multiphasic CT scan should be performed to better characterize most hepatic tumors.

- On CT scans, most lesions (90% according to ***Ichikawa et al; 2000***) show homogeneous enhancement in the hepatic arterial phase. Unfortunately, this feature is not specific to hepatic adenomas, because HCC, hypervascular metastases, and FNH can demonstrate similar enhancement in the hepatic arterial phase.
- Because hepatic adenomas are histologically composed of uniform hepatocytes, most are isoattenuating relative to the healthy liver tissue on nonenhanced scans in the portal venous phase.
- In a fatty liver, hepatic adenomas usually are hyperattenuating.
- Hemorrhage is seen as an area of high attenuation in 40% of patients.
- Fat deposition within adenomas is identified on CT scans in only

approximately 7% of patients.

- Typically, hepatic adenomas have well-defined borders and do not have lobulated contours.
- A low-attenuation pseudocapsule can be seen in as many as 25% of patients.
- Coarse calcifications are seen in only 5% of patients.

Degree of Confidence:

Because conventional hepatocellular carcinoma (HCC) can contain fat and areas of hemorrhage, differentiating hepatic adenoma from HCC is difficult. In the presence of CT scan, signs of portal hypertension and cirrhosis, the diagnosis of HCC is favored, as is the case in the presence of an elevated alpha-fetoprotein level.

As both hepatic adenomas and hypervascular metastases demonstrate intense enhancement on arterial phase imaging, differentiation between them is difficult. The presence of multiple lesions favors a diagnosis of metastatic disease; however, hepatic adenomas can also be multiple, which is termed hepatic adenomatosis. The presence of a primary neoplasm, also favors a diagnosis of metastatic disease.

Although hepatic adenoma and FNH have some similarities clinically and radiologically, certain imaging features can reliably distinguish them. Clinically, both tumors appear in young women. On imaging, hepatic adenoma and focal nodular hyperplasia are usually hypervascular in the hepatic arterial phase. In addition, both tumors usually are isoattenuating relative to the liver on the portal venous phase and on unenhanced images. The presence of **a central scar** is probably the most reliable discriminating feature.

False Positives/Negatives:

Significant overlap is noted between the CT scan appearances of hepatic adenoma, HCC, FNH, and hypervascular metastases, making a definitive diagnosis based on CT imaging criteria alone difficult.

II) *Findings in* Magnetic Resonance Imaging:

Some MRI findings of adenomas are similar to CT findings; however, MRI is usually more sensitive in detecting fat and hemorrhage.

- **On T1-weighted images:** Hepatic adenomas tend to be hyperintense or isointense relative to the liver tissue ***(Paulson et al; 1994).*** High signal intensity probably relates to the presence of fat or, less commonly, to hemorrhage within the lesion. Chemical-shift imaging that shows loss of signal on out-of-phase images can confirm the presence of fat. HCC contains fat in as many as 40% of lesions; therefore, the presence of fat does not help differentiate the lesions.
- **On T2-weighted images:** Hepatic adenomas are most often slightly hyperintense relative to liver tissue. This finding is not specific because many hepatic lesions, including HCC and metastases, are hyperintense.
- **Heterogeneity**, defined as any difference of a signal within a lesion on T1-weighted or T2-weighted images. Heterogeneity relates to the presence of either hemorrhage or necrosis. This finding is not specific as HCC and metastases can bleed and become necrotic. Although uncommon, FNH also can be hemorrhagic.
- A peripheral rim corresponding histologically to a pseudocapsule is seen in 17-31% of patients. Signal characteristics of the rim are variable. Most often, the peripheral rim, when seen, is of low signal intensity on T1-weighted images, is of variable intensity on T2-weighted images, and usually does not enhance.

- ❖ After gadolinium administration, the pattern of enhancement is similar to that of CT scans. Most hepatic adenomas show intense enhancement in the arterial phase and are isointense relative to the liver tissue on delayed imaging.
- ❖ Hepatic adenomas, unlike FNH, do not have a central scar. If a low signal intensity scar is seen on T1-weighted images and the scar enhances after gadolinium is administered, the diagnosis of FNH is strongly favored. A central scar has never been reported in a hepatic adenomas.
- ❖ Mangafodipir trisodium (formerly termed Mn-DPDP) is a hepatobiliary MRI contrast agent that is taken up by hepatocytes and excreted into bile. Because hepatic adenoma, FNH, and HCC all contain hepatocytes, they may demonstrate enhancement with this agent. Metastases and hemangiomas do not contain hepatocytes and do not enhance; therefore, this agent can help differentiate hepatic adenoma, which enhances, from metastases, which do not enhance.
- ❖ Venkatesh et al assessed the potential for MR elastography (MRE) to characterize solid liver tumors ***(Venkatesh et al;2008).***

Degree of Confidence:

Generally, on routine MRI of the liver using T1-weighted, T2-weighted, chemical-shift, and dynamic gadolinium-enhanced imaging, certain hepatic masses can be diagnosed with confidence, whereas others cannot. If a hepatic mass contains a low signal central scar on T1-weighted images that enhance after gadolinium administration, the diagnosis of FNH is fairly certain.

However, overlap exists in the imaging of hepatic adenomas, HCC, and hypervascular metastases such as melanoma. Clinical correlation in

such cases is most helpful. A history of cirrhosis and high alpha-fetoprotein levels favor an HCC diagnosis. A history of melanoma or other primary tumors favors the diagnosis of metastases. In otherwise healthy young women using oral contraceptives, Patients with glycogen storage disease, hemochromatosis, or acromegaly, as well as males on anabolic steroids, the diagnosis of hepatic adenoma is favored.

False Positives/Negatives:

Although most hepatic adenomas are hyperintense relative to normal liver on T1-weighted images, this is not a specific finding. Other hepatic masses, such as HCC, melanoma, metastases, and protein material in hepatic abscess cavities, can be hyperintense as well.

III) ***Findings in*** **Nuclear Imaging:**

A combination of radiotracers may help make the diagnosis of hepatic adenomas in equivocal cases.

- On^{67} Ga scans, hepatic adenomas demonstrate decreased uptake compared with healthy liver tissue, which can be explained by the benign nature of the cells. In contrast, hepatocellular carcinoma (HCC) often demonstrates equivocal or greater^{67} Ga uptake than liver.
- Because hepatic adenomas usually have few or absent Kupffer cells, the lesions show focal defects on sulfur-colloid liver-spleen scans. However, an occasional hepatic adenoma contains enough Kupffer cells to demonstrate normal uptake of sulfur colloid. HCC almost always appears as defects on sulfur-colloid scintigraphy because HCC lacks Kupffer cells. In contrast, FNH contains Kupffer cells and usually demonstrates uptake of sulfur colloid.
- When hepatobiliary agents are used, hepatic adenomas usually demonstrate early uptake with subsequent retention of the radiotracer

because hepatic adenomas do not contain bile ducts; thus, the radiotracer is not excreted by the lesion, which remains "hot" on delayed images. This is in contrast to HCC, which shows focal defects on early scans.

- The use of positron emission tomography (PET) scanning with fluorine-18-fluorodeoxyglucose (^{18}FDG) is useful in the evaluation of many tumors. Malignant tumors usually show uptake of ^{18} FDG, whereas benign tumors do not ***(Patel et al; 1997).***

- When hepatic adenoma is radiologically indistinguishable from HCC and FNH, a combination of radionuclide imaging, including sulfur-colloid, ^{67} Ga, and technetium-99m (^{99m} Tc) pyridoxyl-5-methyltryptophan (PMT) uptake, may help establish the correct diagnosis. Most hepatic adenomas demonstrate decreased ^{67} Ga uptake, decreased sulfur-colloid uptake, and early and retained uptake of hepatobiliary agents.

Degree of Confidence:

Most hepatic adenomas demonstrate decreased ^{67} Ga uptake, decreased colloid uptake, early and retained uptake of hepatobiliary agents, and no uptake on PET scanning; therefore, the diagnosis of hepatic adenoma can often be confidently made with the use of nuclear medicine studies.

False Positives/Negatives:

Cases have been reported of hot hepatic adenomas on PET^{18} FDG scans. In addition, reports exist of hepatic adenomas with enough Kupffer cells to demonstrate uptake on sulfur colloid scans.

IV) *Findings in* Angiography:

In the diagnostic workup of hepatic adenomas, angiography does

not have a significant role. This modality can be helpful for technical reasons when considering resection.

On angiography, *hepatic adenomas* typically appear as hypervascular masses, with the vascular supply arising peripherally. However, hepatic adenomas may be hypovascular (as many as 50%) or have areas of hypovascularity within the mass that correspond to hemorrhage and necrosis.

In contrast, FNH is typically hypervascular with dense capillary blushing. In large lesions, a dilated branch of the hepatic artery can enter the center of the mass and then divide into small branches that radiate in a manner similar to the spokes on a wheel (spoke-wheel appearance). If the spokelike appearance is noted, FNH is the likely diagnosis.

Degree of Confidence:

Angiography is usually not performed for the detection and differentiation of hepatic masses. Angiography can be performed preoperatively to better define the vascular anatomy before resection, although the information can be obtained noninvasively with CT scanning or MR angiography.

Treatment:

I) Medical Care:

- ☒ Patients should stop using oral contraceptives or anabolic steroids;
  - ❋ This allows for regression in the size of the majority of the tumors. Complete resolution is atypical.
  - ❋ The risk of malignant transformation remains even after the contraceptive or steroid use has been discontinued.
- ☒ Symptomatic hepatocellular adenomas may be considered for resection, regardless of size.

- ☒ Pregnancy should be avoided because of the risk of growth and rupture;
  - ❋ *Surgical resection* may be the best option in patients with hepatocellular adenomas who desire to become pregnant.
  - ❋ Resection of large incidental hepatocellular adenomas found during pregnancy may be considered for resection during the second trimester when the risk is lowest.
  - ❋ Ruptured hepatocellular adenomas during pregnancy should be managed with resuscitation and resection.
- ☒ Yearly ultrasound imaging and an assessment of serum AFP levels is a consideration in all patients with hepatocellular adenomas, especially those with multiple lesions or single lesions greater than 5 cm in diameter who do not undergo surgical resection.
- ☒ Immediate abdominal imaging is required for patients with hepatocellular adenomas who present with new or worsened abdominal pain or signs of hemodynamic instability. Emergency hepatic arteriography with embolization should be considered to control bleeding in high-risk surgical candidates.
- ☒ The value of percutaneous fine-needle biopsy for the diagnosis of hepatic adenoma is controversial for 2 reasons: ***first***, histologic studies may lead to misdiagnosis when differentiating hepatic adenoma from focal nodular hyperplasia (FNH); ***second***, a considerable risk of hemorrhage exists when biopsy is performed on these hypervascular tumors.

II) Surgical Care:

- ☒ Due to the increased risk of spontaneous life-threatening hemorrhage and the possible malignant transformation associated

with larger-size tumors or in patients with GSD, elective surgical resection is considered for all lesions greater than 5 cm in diameter. Elective resection should be undertaken only after a reasonable period of observation if OCPs have been discontinued only recently ***(Weimann rt al; 1997).***

- ☒ All patients with significant elevated AFP levels should undergo resection of the tumor regardless of size.
- ☒ The majority can be resected locally or with segmental partial lobectomy;
    - ✵ Elective resection carries approximately 13% morbidity. Mortality is rare.
    - ✵ Complication rates associated with emergency surgery are higher, including a mortality rate of approximately 5-8%.
- ☒ Laparoscopic resection can be used in patients who have small tumors within the anterolateral liver segments.
- ☒ A similar approach also can be considered for pedunculated lesions ***(Ibrahim et al; 2007).***

Follow-up:

Further Outpatient Care:

Yearly ultrasound imaging and an assessment of serum AFP levels is a consideration in all patients with hepatocellular adenomas.

Prognosis:

- ☒ Complete resolution is atypical.
- ☒ The risk of malignant transformation remains as high as 8-13% even after the contraceptive or steroid use has been discontinued.

Imaging: **a.** **b.**

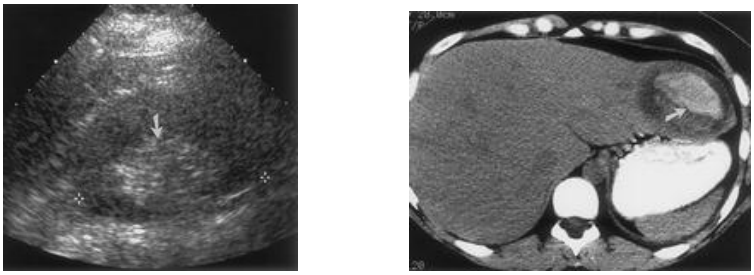


Fig. 15. **Single adenoma in a 33-year-old woman who presented with abdominal pain.**

(a) Transverse US scan of the liver shows a hypoechoic lesion (cursors) with a hyperechoic center (arrow) due to recent hemorrhage.

(b) Unenhanced CT scan shows a hypoattenuating lesion with high-attenuation blood centrally (arrow).

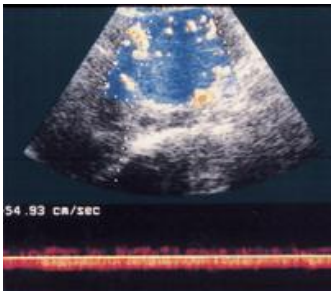


Fig. 16**. Single adenoma in a 37-year-old woman who presented with abdominal pain. The patient had been using oral contraceptives for the past 10 years. Color Doppler US image of peri- and intratumoral vessels shows a typically flat continuous waveform. (Courtesy of Riccardo Lencioni, MD, Division of Diagnostic and Interventional Radiology, University of Pisa, Italy.).** **a.** **b.**

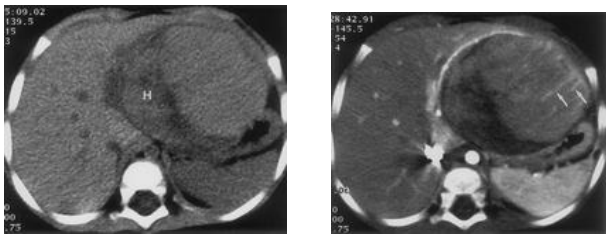


Fig. 17. **Palpable epigastric mass in a 4-year-old girl.**

(a) Unenhanced CT scan shows a large mass with hemorrhage (*H*).

(b) Arterial-phase CT scan shows the mass with large penetrating vessels (arrows).

a. **b.** **c.**

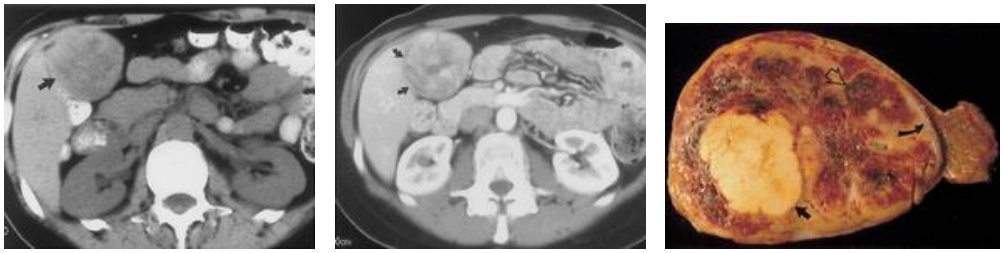


Fig. 18. **Single adenoma in a 49-year-old woman. The adenoma was discovered incidentally at laparoscopic surgery.**

(a) Unenhanced CT scan shows a 5-cm-diameter, exophytic, slightly hypoattenuating tumor in the right lower lobe of the liver (arrow).

(b) On an arterial-phase CT scan, the tumor shows heterogeneous enhancement. Note the enhancing incomplete pseudocapsule (arrows).

(c) Photograph of the resected specimen shows a well-circumscribed mass with extensive hemorrhage (open arrow), a partial capsule (curved arrow), and foci of yellow-tan tissue (straight solid arrow). These tissue foci demonstrated markedly increased cytoplasmic lipid content at histologic analysis.

a. **b.** **c.**

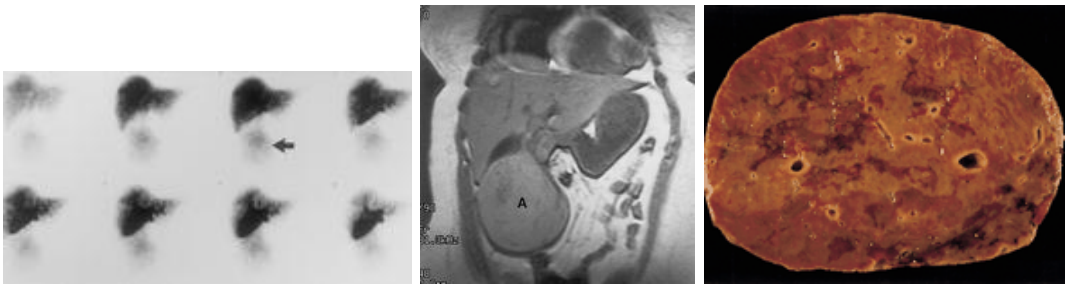


Fig. 19. **Large, pedunculated hepatic adenoma in a 36-year-old woman who presented with right upper quadrant abdominal pain.**

(a) Tc-HIDA scan demonstrates faint activity below the inferior margin of the liver (arrow).

(b) Coronal T1-weighted spin-echo MR image shows a pedunculated mass arising from the inferior margin of the liver (*A*).

(c) Photograph of the resected specimen shows a well-circumscribed, brown, hemorrhagic mass, with some vessels cut in a transverse plane. The adenoma was almost completely Extrahepatic.

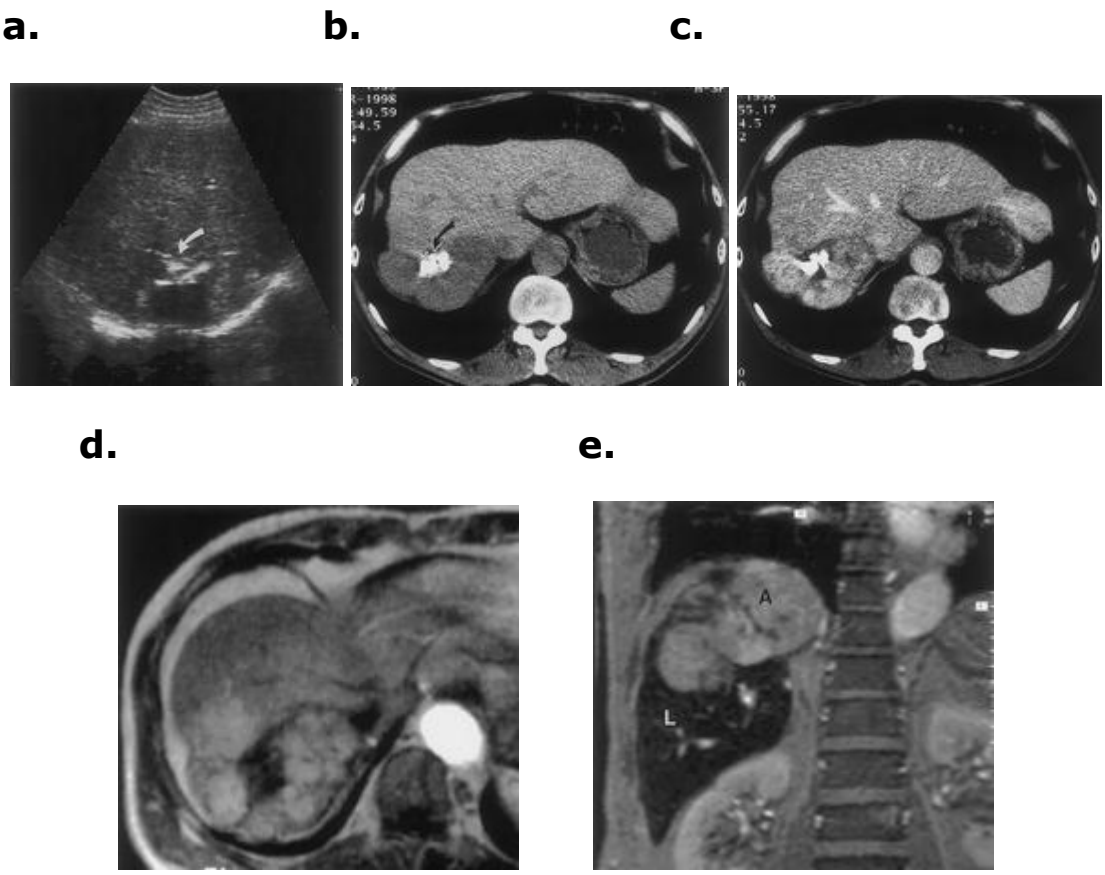


Fig. 20. **Calcified adenoma in a 59-year-old man.**

(a) Transverse US scan of the right lobe of the liver shows hyperechoic lesions with acoustic shadowing (arrow).

(b) Unenhanced CT scan shows a mass in the right lobe with a large central calcification (arrow).

(c) Portal venous-phase CT scan shows heterogeneous enhancement of most of the adenoma. Calcifications are noted within hypoattenuating cystic areas.

(d) Arterial-phase gadolinium-enhanced MR image shows heterogeneous enhancement of the adenoma and a signal void representing the central calcification.

(e) Coronal MR image obtained following administration of superparamagnetic iron oxide shows the normal liver (*L*) with decreased signal intensity. The adenoma (*A*) remains unaffected.

a. **b.** **c.**

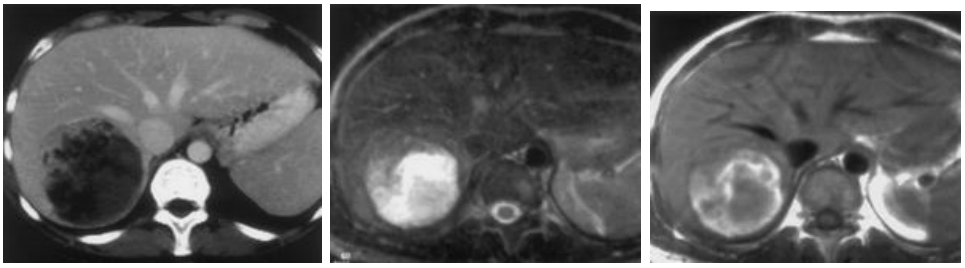


Fig. 21. **Single adenoma in a 42-year-old woman.**

(a) Portal venous-phase CT scan shows a poorly enhancing, spheric mass without obvious hemorrhage.

(b) On a T2-weighted MR image, the mass appears heterogeneously hyperintense.

(c) T1-weighted MR image shows the mass with heterogeneous hyperintensity due to hemorrhage.

a . ***b.***

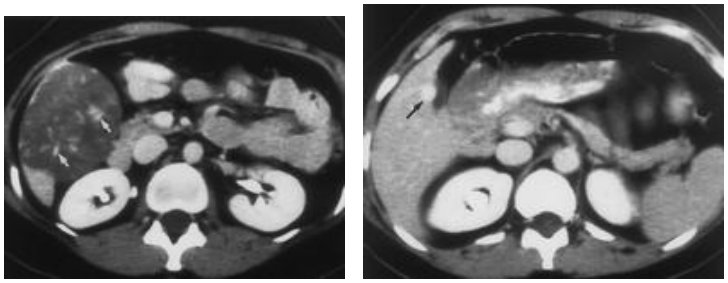


Fig. 22. **Single adenoma in a 40-year-old woman. The adenoma was discovered at hysterectomy.**

(a) Axial portal venous-phase CT scan through the right lower lobe of the liver shows a large mass with large internal vessels (arrows).

(b) Axial CT scan obtained at a higher level shows a portion of a large draining vein (arrow) that emptied into the right hepatic vein.

a. ***b.*** ***c.*** ***d.***

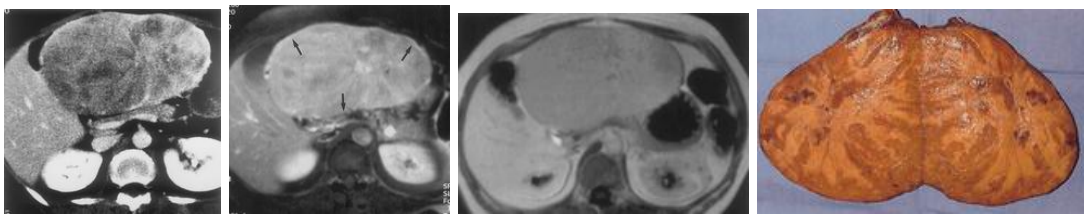


Fig. 23. **Large single adenoma in a 45-year-old woman.**

(a) Axial portal venous-phase CT scan shows a large adenoma replacing the lateral segment of the left hepatic lobe. The mass is heterogeneously enhanced.

(b) Axial fat-saturated T1-weighted MR image obtained following intravenous bolus injection of gadopentetate dimeglumine shows an enhancement pattern similar to that seen at CT. Note the peripheral hyperintense rim corresponding to the fibrous capsule (arrows).

(c) On an axial MR image obtained 1 hour after intravenous administration of Gd-BOPTA, the liver and kidney show increased signal intensity. The adenoma fails to enhance due to decreased uptake and excretion of this hepatobiliary contrast agent.

(d) Photograph of the resected specimen (cut section opened in a "bivalve" fashion) reveals that bands of different tumor constituents (mostly due to varying lipid content) account for the heterogeneity seen at imaging.

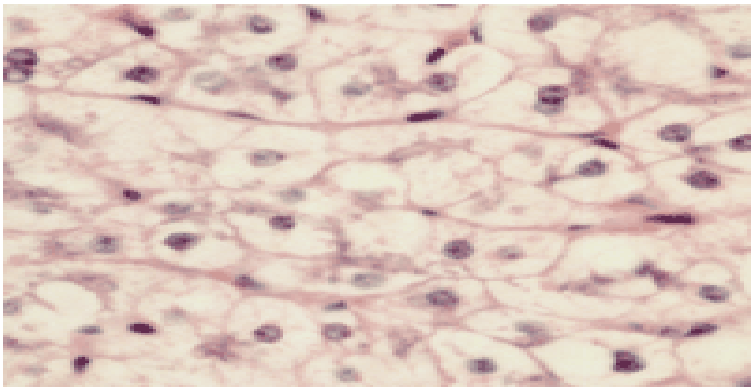


Fig. 24.**Adenoma. High-power photomicrograph (hematoxylin-eosin stain) of a core-needle biopsy specimen shows an adenoma composed of disorganized hepatocyte cords. The individual cells resemble normal hepatocytes but contain large amounts of lipid and glycogen, which accounts for the pale cytoplasm.**

Other Solid Tumors:

a) Hepatic Granulomas:

Hepatic granulomas have numerous causes and are usually asymptomatic. However, the underlying disorder may cause extrahepatic manifestations, hepatic inflammation, fibrosis, portal hypertension, or a combination.

Diagnosis is based on liver biopsy, but biopsy is necessary only if a treatable underlying disorder (eg, infection) is suspected or if other liver disorders need to be ruled out. Treatment depends on the underlying disorder.

Hepatic granulomas, although sometimes insignificant, more often reflect clinically relevant disease. The term granulomatous hepatitis is often used to describe the condition, but the disorder is not true hepatitis, and the presence of granulomas does not imply hepatocellular inflammation.

AEtiology:

Hepatic granulomas have many causes; *drugs* and *systemic disorders* (often infections) are more common causes than primary liver disorders. Infections must be identified because they require specific treatments. *TB* and *schistosomiasis* are the most common infectious causes worldwide; fungal and viral causes are less common.

Sarcoidosis is the most common noninfectious cause; the liver is involved in about 2/3 of patients. Occasionally, clinical manifestations of sarcoidosis are predominantly hepatic ***(Ishak KG. 1998).***

Granulomas are much less common in primary liver disorders; primary biliary cirrhosis is the only important cause. Small granulomas occasionally occur in other liver disorders but are not clinically significant.

Idiopathic granulomatous hepatitis:

Is a rare syndrome of hepatic granulomas with recurrent fever, myalgias, fatigue, and other systemic symptoms, which often occur intermittently for years. Some experts believe it is a variant of sarcoidosis ***(Simon et al; 1973).***

Causes of Hepatic Granulomas

i. **Drugs :** Allopurinol, phenylbutazone, quinidine, sulfonamides ***(Farrell GC. 1995).***

ii. **Infections** :

   a. **bacterial :** Actinomycosis, brucellosis, cat-scratch fever, syphilis, TB, other mycobacterial infections, tularemia, Q fever**.**

   b. **fungal:** Blastomycosis, cryptococcosis, histoplasmosis**.**

   c. **parasitic :** Schistosomiasis, toxoplasmosis, visceral larva migrans **.**

   d. **viral infections**

iii. **Liver disorders :** Primary biliary cirrhosis**.**

iv. **Systemic disorders :** Hodgkin's lymphoma, polymyalgia rheumatica, other connective tissue disorders, sarcoidosis**.**

Pathophysiology:

A granuloma is a localized collection of chronic inflammatory cells with epithelioid cells and giant multinucleated cells. Caseation necrosis or foreign body tissue (eg, schistosome eggs) may be present.

Most granulomas occur in the parenchyma, but in primary biliary cirrhosis, granulomas may occur in the hepatic triads.

Granuloma formation is incompletely understood. Granulomas may develop in response to poorly soluble exogenous or endogenous irritants. Immunologic mechanisms are involved ***(Denk et al; 1994).***

Hepatic granulomas rarely affect hepatocellular function. However, when granulomas are part of a broader inflammatory reaction involving

the liver (eg, drug reactions, infectious mononucleosis), hepatocellular dysfunction is present.

Sometimes inflammation causes progressive hepatic fibrosis and portal hypertension, typically with schistosomiasis and occasionally with extensive sarcoidal infiltration.

Symptoms and Signs:

Granulomas themselves are typically asymptomatic; even extensive infiltration usually causes only minor hepatomegaly and little or no jaundice. Symptoms, if they occur, reflect the underlying condition (eg, constitutional symptoms in infections, hepatosplenomegaly in schistosomiasis).

Diagnosis:

- Liver function tests
- Imaging
- Biopsy

Hepatic granulomas are suspected in patients with:

- ♦ Conditions that commonly cause granulomas,
- ♦ Unexplained hepatic masses found during imaging tests,
- ♦ Occasionally, when an imaging test is done to evaluate asymptomatic elevations in liver enzymes, particularly alkaline phosphatase.

When granulomas are suspected, liver function tests are usually done, but results are nonspecific and are rarely helpful in diagnosis.

Alkaline phosphatase (and γ–glutamyl transferase) is often mildly elevated but occasionally may be markedly elevated.

Other test results may be normal or abnormal, reflecting additional hepatic damage (eg, widespread hepatic inflammation due to a drug reaction).

Usually, imaging tests, such as ultrasonography, **CT**, or **MRI**, are not diagnostic; they may show calcification (if granulomas are long-standing) or filling defects, particularly with confluent lesions.

Diagnosis is based on **liver biopsy**. However, biopsy is usually indicated only to diagnose treatable causes (eg, infections) or to rule out from nongranulomatous disorders (eg, chronic viral hepatitis).

Biopsy sometimes detects evidence of the specific cause (eg, schistosomal ova, caseation of TB, fungal organisms). However, other tests (eg, cultures, skin tests, laboratory tests, imaging tests, other tissue specimens) are often needed ***(Lefkowitch JH 1999).***

In patients with constitutional or other symptoms suggesting infection (eg, FUO), specific measures are taken to increase the diagnostic sensitivity of biopsy for infections; eg, a portion of the fresh biopsy specimen is sent for culture, or special stains for acid-fast bacilli, fungi, and other organisms are used. Often, cause cannot be established.

Prognosis:

Hepatic granulomas caused by drugs or infection regress completely after treatment.

Sarcoid granulomas may disappear spontaneously or persist for years, usually without causing clinically important liver disease.

Progressive fibrosis and portal hypertension (sarcoidal cirrhosis) rarely develop.

In *schistosomiasis*, progressive portal scarring (pipestem fibrosis) is typical; liver function is usually preserved, but marked splenomegaly and variceal hemorrhage can occur.

Treatment:

Treatment is directed at the underlying disorder. When the cause is unknown, treatment is usually withheld, and follow-up with periodic liver function tests is instituted.

However, if symptoms of TB (eg, prolonged fever) and deteriorating health occur, empiric antituberculous therapy may be justified.

Corticosteroids may benefit patients with progressive hepatic sarcoidosis, although whether these drugs prevent hepatic fibrosis is unclear. However, corticosteroids are not indicated for most patients with sarcoidosis and are warranted only if TB and other infections can be excluded confidently ***(Steven et al; 2007).***

Imaging:

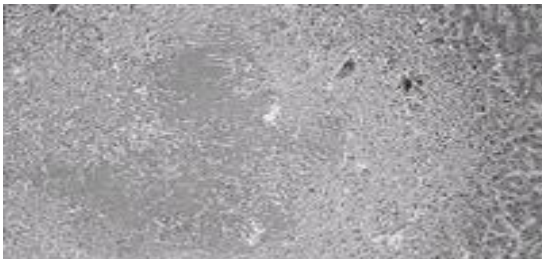


Fig. 25. **Liver showing a portion of a large caseating granuloma from a patient with miliary mycobacterium tuberculosis. Several Langhans' giant cells are also seen.**

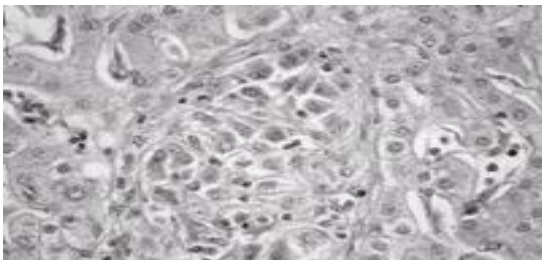


Fig. 26. **Liver from an HIV/AIDS patient infected with *Mycobacterium avium intercellulare*, showing a granuloma composed of epithelioid cells which contain large numbers of micro-organisms. (Diastase/periodic acid–Schiff stain, total magnification 100.).**

b) Macroregenerative Nodule

Pathogenesis and Pathology:

Macroregenerative nodule (MRN) was previously classified as adenomatous hyperplasia or high-grade dysplastic nodule (.1 cm) ***(Hussain et al; 2002).***

MRN occurs on the background of the cirrhotic liver, acute massive or submassive necrotic liver. Nowadays, MRNs are more frequently detected in liver explants after orthotropic liver transplantation ***(Gurkan et al; 2001).***

Clinical importance of MRN is its malignant transformation to HCC, although it is not clear how what percentage of MRN will progress to malignancy. The reported prevalence of MRN varies between 14.2% and 25% on autopsy series ***(Gurkan et al; 2001).***

In acute massive or submassive necrosis, remaining hepatic parenchyma shows compensatory lobular hyperplasia after parenchymal loss. In cirrhotic liver, the hyperplastic reactions occur as a result of even a larger amount of cell loss. Regenerating islets of viable cells are formed between destructed areas, and these islets make up the nodular structures ***(Colombo M. 2002).***

Macroscopically, MRN has a greener or paler color compared with the surrounding cirrhotic liver. As compared with HCC, MRN has lower proliferation indices, which is no greater than three-cell thickness ***(Brunt EM. 2001).***

At times, MRN may demonstrate ischemic coagulative necrosis and hemorrhage, nuclear crowding, and microacinal formation that herald the development of HCC. MRN usually has variable atypia. More specifically, MRN without atypia is classified as Type I and MRN with atypia as Type II.

Clinical Presentation:

Patients have no specific symptoms since MRN is usually discovered by imaging studies in patients with cirrhosis or advanced fibrosis for evaluation of HCC.

Liver function test with viral markers study shows the etiology and severity of underlying liver disease.

Imaging:

MRN is rarely detected on screening ***US (Rode et al; 2001).***

On ***CT***, the presence of MRN can be suggested by nodular hepatic contour, and nodules are iso-attenuating to surrounding liver during arterial and portal phases ***(de Ledinghen et al; 2002).***

On ***MRI***, lesions show variable signal intensities on T1-weighted images and typically hypointensity on T2-weighted images with no enhancement on arterial enhanced phase. These are distinguishable features from HCC, which typically are hyperintense on T2-weighted images with strong enhancement during the arterial phase ***(Rode et al; 2001&Krinsky et al; 2001).***

Sparse central or peripheral blood supply is found on ***angiography*** without neovascularity.

HCC emerging from MRN can be demonstrated as nodule-in-nodule pattern on imaging studies due to their histologic uneven growth ***(Serra et al; 1999).***

Management and Summary:

MRN is a benign but premalignant lesion found in cirrhotic or fibrotic livers. Imaging findings are not characteristic, but MRI findings are useful for the differentiation from HCC.

Because of its malignant potential, surgical resection of MRN is sometimes advocated, especially in those with atypia. Optimal management of MRN remains unknown pending ongoing investigation.

c) Mesenchymal Hamartoma

Mesenchymal hamartoma of the liver is an uncommon benign lesion composed of bile ducts, immature mesenchymal cells, and hepatocytes ***(Cook et al; 2002).***

Most of them are diagnosed during childhood, although a few cases have been reported in adults ***(Brkic et al; 2003).***

The clinical presentation is nonspecific, and imaging findings reveal solid or multicystic lesions ***(Papastratis et al; 2000).***

Although hamartoma can be diagnosed by percutaneous biopsy, diagnosis is usually established after surgical excision.

d) Focal Fatty Change

Hepatic steatosis is generally a diffuse process, but focal distribution of fat is quite common in the liver called focal fatty change ***(Wanless IR. 2002).***

The pathogenesis is not well understood, but regional hypoxia of hepatic tissue is thought to play a role according to one theory ***(Zeppa et al; 2002).***

The majority of patients have underlying disease such as diabetes, obesity, and malnutrition.

Lesions are often discovered incidentally on imaging studies and characteristically show a fan-shaped or geographic pattern mainly in subcapsular areas or regions adjacent to the falciform ligament ***(Itai et al; 2002).***

Focal fatty change can be found as single or multiple lesions with variable sizes in a few centimeters up to 10 cm. These tumor-like lesions may be mistaken for other hepatic tumors, and liver biopsy is often required for a definitive diagnosis ***(Zeppa et al; 2002).***

e) Lipomatous Tumor

Lipomatous tumors such as hepatic angiomyolipoma or hepatic lipoma are very rare benign tumors. Patients are usually asymptomatic, and lesions are often encountered in patients with tuberous sclerosis ***(Mergo et al; 1998).***

As their names imply, on the imaging studies, lipoma shows uniform fat component, whereas angiomyolipoma also contains intratumoral vessel and smooth muscle component. Atypical cases should be carefully differentiated from other hypervascular tumors including HCC, FNH, and hemangioma ***(Yan et al; 2002).***

Fine-needle aspiration is occasionally required and reveals fat cells, epithelioid smooth muscle cells,and blood vessels***(Hogemann etal;2001).*** The prognosis is good, and surgical resection may be needed if patients have symptoms related to mass effect***(Ren et al;2003&Yeh et al ;2001).***

f) Inflammatory Pseudotumor

Inflammatory pseudotumor is an extremely rare benign hepatic tumor. It has the appearance of a malignant tumor but has a benign histology and clinical course ***(Sakai et al; 2002).***

The etiology is unclear, but underlying infectious agents are strongly suggested as the pathologic process ***(Koea et al; 2003).***

The clinical presentation is nonspecific. Patients may have fever, malaise, weight loss, and symptoms related to a mass effect.

Routine imaging procedures are not sufficient to make the diagnosis, and a biopsy is necessary to differentiate it from other tumors ***(Choi et al; 2003).*** Histologic examination reveals myofibroblasts, polyclonal plasma cell, and fibrous tissue. The course of the disease is unpredictable. In most of the reported cases, the patients underwent resection ***(Biecker et al; 2003).***

♦ Benign focal cystic lesions of the liver:

The term hepatic cyst usually refers to solitary nonparasitic cysts of the liver, also known as simple cysts. However, several other cystic lesions must be distinguished from true simple cysts.

Cystic lesions of the liver include:

1. **Simple cysts.**
2. **Parasitic or hydatid (echinococcal) cysts.**
3. **Cystic tumors.**
4. **Abscesses.**

These conditions can usually be distinguished on the basis of the patient's symptoms and the radiographic appearance of the lesion.

Ductal cysts, choledochal cysts, **and** ***Caroli disease*** are differentiated from hepatic cysts by involvement of the bile ducts.

1.Simple cysts:

Etiopathogenesis:

The cause of simple liver cysts is not known, but they are believed to be congenital in origin.

The cysts are lined by biliary-type epithelium and perhaps result from progressive dilatation of biliary microhamartomas. Because these cysts seldom contain bile, the current hypothesis is that the microhamartomas fail to develop normal connections with the biliary tree.

Typically, the fluid within the cyst has an electrolyte composition that mimics plasma. Bile, amylase, and white blood cells are absent. The cyst fluid is continually secreted by the epithelial lining of the cyst. For this reason, needle aspiration of simple cysts is not curative.

Presentation:

a. Simple cysts generally cause no symptoms but may produce dull right upper quadrant pain if large in size.

b. Patients with symptomatic simple liver cysts may also report abdominal bloating and early satiety.

c. Occasionally, a cyst is large enough to produce a palpable abdominal mass.

d. Jaundice caused by bile duct obstruction is rare, as is cyst rupture and acute torsion of a mobile cyst.

e. Patients with cyst torsion may present with an acute abdomen.

f. When simple cysts rupture, patients may develop secondary infection, leading to a presentation similar to a hepatic abscess with abdominal pain, fever, and leukocytosis.

Laboratory Studies:

The evaluation of a patient with a simple liver cyst involves carefully recording patient history and performing a physical examination plus an imaging study, such as an abdominal CT scan, to define the anatomy of the cyst. Patients with simple hepatic cysts require little preoperative laboratory workup.

Liver function test results, such as transaminases or alkaline phosphatase, may be mildly abnormal, but bilirubin, prothrombin time, and activated partial thromboplastin times are usually within the reference range.

Imaging Studies:

Before the widespread availability of abdominal imaging techniques, including ultrasonography and computed tomography scans.

Liver cysts were diagnosed only when they grew to an enormous size and became apparent as an abdominal mass or as an incidental finding during laparotomy. Today, imaging studies often reveal asymptomatic lesions incidentally.

The clinician has a number of options for imaging the liver in patients with hepatic cysts. ***Ultrasonography*** is readily available, noninvasive, and highly sensitive, ***Computed tomography*** scan is also highly sensitive and is easier for most clinicians to interpret, particularly for treatment planning. ***MRI, Nuclear medicine scanning***, ***Hepatic angiography*** has a limited role in the evaluation of hepatic cysts.

Simple cysts have a typical radiographic appearance. They are thin walled with a homogenous low-density interior.

A practical problem in the evaluation of a patient with a cystic hepatic lesion is differentiating cystic neoplasms from simple cysts. *Cystic neoplasms* tend to have thicker, irregular, hypervascular walls, whereas simple cysts tend to be thin walled and uniform. *Simple cysts* tend to have homogenous low-density interiors, whereas neoplastic cysts usually have heterogeneous interiors with septa and papillary extrusions.

Other Tests:

Other tests are generally not necessary in the evaluation of hepatic cysts. Percutaneous aspiration should be avoided because the laboratory and cytologic evaluation of the simple cyst fluid is nondiagnostic.

Histologic Findings:

Histologic assessment of the excised cyst wall should be routinely undertaken to identify the presence of an unsuspected neoplasm, such as cystadenoma.In simple cysts, histology of the cyst wall generally reveals a layer of simple cuboidal epithelium.

Treatment:

- **Indications:**

Treatment of solitary nonparasitic cysts of the liver is indicated only in symptomatic patients. Asymptomatic patients do not require therapy because the risk of developing complications related to the lesion is lower than the risk associated with treatment.

- **Contraindications**

Contraindications to treatment of symptomatic liver cysts relate mainly to underlying comorbid illnesses that increase surgical risk. In particular, congestive heart failure and liver failure with portal hypertension and ascites increase operative risk. Symptoms suggestive of angina or transient ischemic attacks should lead to further preoperative diagnostic studies to identify significant coronary or carotid arterial stenoses ***(Morino et al; 1994).***

I) Medical Therapy:

No medical therapy has proven effective in reducing the size of simple hepatic cysts. Percutaneous aspiration under ultrasound or CT guidance is technically simple but has been abandoned because the recurrence rates are nearly 100%.

Aspiration combined with sclerosis with alcohol or other agents has been successful in some patients but has high failure and recurrence rates. Successful sclerosis depends on complete decompression of the cyst and apposition of the cyst walls. This is not possible if the cyst wall is thickened or if the cyst is large.

Percutaneous catheters should not be placed to drain simple cysts because the cavity becomes contaminated, leading to the development of hepatic abscess. Unlike the typical pyogenic hepatic abscess, this problem

is difficult to resolve with repeated catheter placements because of continued secretion from the cyst epithelium.

II) Surgical Therapy:

Most patients with simple cysts are asymptomatic and require no treatment. When the cysts become large and cause symptoms, such as pain, treatment is warranted.

Surgical treatment of simple liver cysts involves "unroofing" the cyst by excising the portion of the wall that extends to the surface of the liver. Excision of this portion of the cyst wall at the liver surface produces a saucer-type appearance in the remaining cyst so that any fluid secreted from the remaining epithelium leaks into the peritoneal cavity where it can be absorbed ***(Fabiani et al; 2005& Taylor et al; 1997).***

Although ablating the remaining epithelium with electrocautery or an argon beam coagulator is possible, this generally is not required because the volume of fluid secreted each day can be absorbed by the peritoneum without any consequence.

Historically, treatment of symptomatic hepatic cysts required laparotomy, but, today, cyst unroofing can be successfully performed laparoscopically ***(Fiamingo et al; 2003).***

Anecdotal reports of laparoscopic treatment became common by the mid 1990s, and the laparoscopic approach is currently considered the standard of care. When compared to laparotomy, this technique is associated with less postoperative pain and disability, shorter duration of hospital stay, and superior cosmetic results ***(Hansen et al; 1997).***

Follow-up:

Following successful laparoscopic unroofing of a simple liver cyst, the patient is seen at a follow-up visit within 2 weeks and again 6 weeks

after surgery to assess symptomatic relief and to identify complications, such as wound infection or ascites. Routine radiographic studies are not obtained unless symptoms recur.

Complications:

Complications of laparoscopic unroofing of simple liver cysts are uncommon. Trocar site infection is a rare occurrence.

Unexpected leakage of bile from the cut edges of the cyst can lead to a subhepatic or subphrenic fluid collection or, rarely, bile ascites.

Outcome and Prognosis:

- Several small series of patients undergoing laparoscopic unroofing of simple hepatic cysts have reported cure rates of 90% or higher.

Future and Controversies:

In patients with simple liver cysts, the general agreement is that laparoscopic unroofing offers the best balance between efficacy and safety.

Imaging:

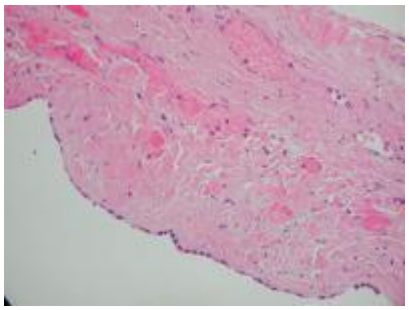


Fig. 27: Histology demonstrating biliary epithelium lining simple cyst.

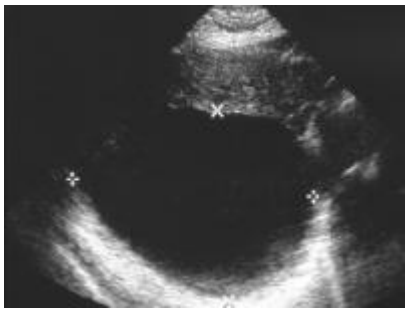


Fig. 28: Ultrasound appearance of a patient with a large simple hepatic cyst.

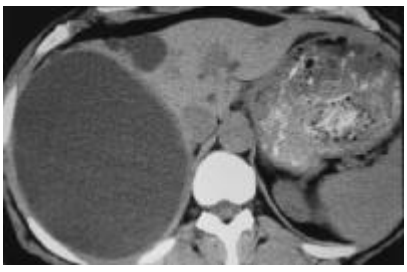


Fig. 29: CT scan appearance of a large hepatic cyst.

2. Hydatid Cysts

Hydatid disease is a parasitic infestation by a tapeworm of the genus *Echinococcus.* Specially; *Echinococcus granulosus,* causing cystic echinococcosis (CE).

Aetiopathogenesis:

Hydatid cysts are caused by infestation with the parasite *Echinococcus granulosus*. This parasite is found worldwide, but it is particularly common in areas of sheep and cattle farming.

The adult tapeworm lives in the digestive tract of carnivores, such as dogs or wolves. Eggs are released into the stool and are inadvertently ingested by the intermediate hosts, such as sheep, cattle, or humans. The egg larvae invade the bowel wall and mesenteric vessels of the intermediate host, allowing circulation to the liver ***(Flisser A. 1998).***

In the liver, the larvae grow and become encysted. The hydatid cyst develops an outer layer of inflammatory tissue and an inner germinal membrane that produces daughter cysts. When carnivores ingest the liver of the intermediate host, the scolices of the daughter cysts are released in the small intestines and grow into adult worms, thus completing the life cycle of the worm ***(Pedrosa et al; 2000).***

Frequency:

Despite the rise in occurrence, echinococcosis remains a very rare disease (<1 case per 1 million inhabitants) in the continental United States. **Internationally;** The endemic areas are the Mediterranean countries, the Middle East, the southern part of South America, Iceland, Australia, New Zealand, and southern parts of Africa; the latter 5 are intensive endemic areas. The incidence of CE in endemic areas ranges from 1-220 cases per 100,000 inhabitants.

Mortality/Morbidity:

Morbidity is usually secondary to free rupture of the echinococcal cyst (with or without anaphylaxis), infection of the cyst, or dysfunction of affected organs; (e.g, biliary obstruction or cirrhosis).

In CE, mortality is secondary to anaphylaxis, systemic complications of the cysts (e.g, sepsis, cirrhosis, or operative complications.

Race:

Because of the restricted geographic distribution of the echinococcal worms, persons of certain races are affected more commonly than others; however, the parasite has the capability of infecting persons of all races equally.

Sex:

No sexual predilection is recognized.

Age:

The cysts grow slowly, and a cyst is rarely diagnosed during childhood or adolescence unless the brain is affected. CE is a disease of younger adults, with an average age at diagnosis of 30-40 years.

Presentation:

Many hydatid cysts remain asymptomatic, even into advanced age. Parasite load, the site, and the size of the cysts determine the degree of symptoms. A history of living in or visiting an endemic area must be established. Also, exposure to the parasite through the ingestion of foods or water contaminated by the feces of a definitive host must be determined. Theoretically, echinococcosis can involve any organ. The liver is the most common organ involved ***(Filippou et al; 2007).***

In CE, symptoms can be produced by mass effect or cyst complications.

☒ Most ***symptomatic cysts*** are larger than 5 cm in diameter. Symptoms due to pressure usually take a long time to manifest.

- In the liver, the pressure effect of the cyst can produce symptoms of obstructive jaundice and abdominal pain.
- With biliary rupture, the classic triad of biliary colic, jaundice, and urticaria is observed.
- Passage of hydatid membranes in the emesis (hydatid emesia) and passage of membranes in the stools (hydatid enterica) may occur rarely.

☒ ***Secondary complications*** may occur as a result of infection of the cyst or leakage of the cyst.

- Minor leaks: lead to increased pain and a mild allergic reaction characterized by flushing and urticaria.
- Major rupture: leads to a full-blown anaphylactic reaction, which is fatal if not treated promptly. A rupture into the biliary tree can lead to obstruction by the daughter cysts, producing cholangitis.

☒ ***Infection of the cyst*** can occur either as a primary infection or as a secondary infection following an episode of a leak into the biliary tree a cystobiliary fistula. Symptoms range from mild fever to full-blown sepsis.

☒ Symptomatology is that of progressive liver dysfunction that ultimately leads to liver failure. The progression can occur over weeks, months, or years.

Physical examination:

Physical examination findings from patients with echinococcosis are nonspecific.

The findings are related to the effect of the cyst on the anatomy or the function of the liver and to an acute allergic reaction ***(von Sinner et al; 1991).***

Skin*:*

- Jaundice could be a sign of biliary obstruction. Spider angiomas are a sign of portal hypertension secondary to either biliary cirrhosis or obstruction of the inferior vena cava.
- Urticaria and erythema may be seen.

Vital signs:

- Fever could be a sign of secondary infection or allergic reaction.
- Hypotension is observed with anaphylaxis secondary to a cyst leak.

Abdomen:

- The most common sign is abdominal tenderness.
- Right hypochondrial mass mostly tender.
- Hepatomegaly may be present or a mass may be felt.
- Tender hepatomegaly is a sign of secondary infection of the cyst, especially when coupled with fever and chills.
- Ascites is rare.
- Splenomegaly can be the result of either splenic echinococcosis or portal hypertension.

Differential Diagnoses:

1. Abdominal abceses.
2. Inferior vena caval thrombosis.
3. Acute liver failure.
4. Intra abdominal sepsis.
5. Biliary colic.
6. Liver abcess.
7. Biliary obstruction.
8. Budd-chiari-syndrome.
9. Portal hypertention.
10. Cysticercosis.
11. Pyogenic hepatic abscess.
12. Teratoma cystica.
13. Primary hepatic carcinoma.
14. Tuberculosis.
15. Hepatic Cysts.
16. Biliary cirrhosis
17. Immediate hypersensitivity reactions.

Laboratory Studies:

The results of routine laboratory blood work are nonspecific. Liver involvement may be reflected in:

- Elevated bilirubin or alkaline phosphatase level.
- Leukocytosis may suggest infection of the cyst.
- Eosinophilia is present in 25% of all persons who are infected, while hypogammaglobinemia is present in 30%.
- The indirect hemagglutination test and the enzyme-linked immunosorbent assay (ELISA) have a sensitivity of 90% in hepatic echinococcosis and are the initial screening tests of choice ***(Liu et al; 1992).*** The ELISA test is useful in follow-up to detect recurrence.
- Immunodiffusion and immunoelectrophoresis demonstrate antibodies to antigen 5 and provide specific confirmation of reactivity ***(Williams et al; 1971).***

Imaging Studies : *(von Sinner et al; 1991).*

I) Plain films:

In CE, findings from plain films of the chest, abdomen, or any other involved site are, at best, nonspecific and mostly nonrevealing. A thin rim of calcification delineating a cyst is suggestive of an echinococcal cyst ***(Pedrosa et al; 2000).***

II) Ultrasound:

Ultrasonography helps in the diagnosis of hydatid cysts when the daughter cysts and hydatid sand are demonstrated. The accuracy of ultrasound evaluations remains operator-dependent.

III) CT scan:

CT scan has an accuracy of 98% and the sensitivity to demonstrate the daughter cysts. It is the best test for the differentiation of hydatid from amebic and pyogenic cysts in the liver.

IV) MRI:

Images show the cysts adequately, but MRI offers no real advantage over CT scan.

Other Tests:

Casoni test:

An intradermal skin test was used and had a sensitivity of 70%. It is now largely abandoned because of its low sensitivity, low accuracy, and potential for severe local allergic reaction.

Procedures: Endoscopic retrograde cholangiopancreatography: It is both diagnostic and therapeutic in patients with intrabiliary rupture of a hydatid cyst, in whom sphincterotomy can be performed.

Treatment *(Dziri et al; 2004).*:

I. Medical Care:

In CE, surgery remains the primary treatment and the only hope for complete cure. Better forms of chemotherapy and newer methods, such as the puncture, aspiration, injection, and reaspiration (PAIR) technique are now available but need to be tested.

Currently, indications for these modes of therapy are restricted. Consider risks and benefits, indications, and contraindications for each case before making a decision regarding the type and timing of surgery ***(Filippou et al; 2007).***

i. Chemotherapy in CE:

❖ ***Indications****:* Indicated in patients with primary liver cysts that are inoperable (because of location or medical condition), patients with cysts in 2 or more organs, and peritoneal cysts.

❖ ***Contraindications:*** Early pregnancy, bone marrow suppression, chronic hepatic disease, large cysts with the risk of rupture, and inactive or calcified cysts are contraindications.

❖ ***Chemotherapeutic agents****:* Two benzimidazoles are used, albendazole and mebendazole.

1) Albendazole:

Decreases ATP production in worm, causing energy depletion, immobilization, and finally, death ***(Taylor et al; 1988).*** Orally administered broad spectrum anthelmintic with poor aqueous solubility. Poorly absorbed from GI tract but metabolized quickly to albendazole sulfoxide, which is easily absorbed. Systemic activity is attributed to first metabolite. Plasma level is noted to rise significantly when ingested after high-fat meal.

Albendazole has been found ineffective in the treatment of primary liver cysts in patients who are surgical candidates ***(Kapan et al; 2008).***

Dosing:

Adult: 10-15 mg/kg/d PO divided bid for 28 d, then 14 d washout period, or for 4 d prior to surgery; then 1 mo postoperatively as adjunct. The optimal period of treatment ranges from 3-6 months, with no further increase in the incidence of adverse effects if this period is prolonged.

Pediatric: Administer as in adults (limited in children <6 y)**.**

Interactions*:*

Coadministration with carbamazepine may decrease efficacy; dexamethasone (8-mg doses), cimetidine (10 mg/kg/d), and praziquantel (40 mg/kg) may increase toxicity; carefully monitor theophylline levels.

Contraindications:

Documented hypersensitivity.

Precautions:

Discontinue if LFT results increase significantly (resume when levels decrease to pretest values); reports of hepatic failure in impaired liver function; reversible WBC count reductions in 1% of patients. Pregnancy: Caution in first trimester of pregnancy. C- Fetal risk.

2) Mebendazole (Vermox):

Causes worm death by selectively and irreversibly blocking uptake of glucose and other nutrients in susceptible adult intestine where helminths dwell. Broad spectrum synthetic anthelmintic.

Dosing:

Adult: 40-50 mg/kg/d PO for 3-6 mo (primary mode of therapy) or for 4 d prior to surgery and then 1 mo postoperatively as adjunct.

***Pediatric*:** < 2years: Not established & >2 years: as in adults.

Interactions:

Carbamazepine and phenytoin may decrease effects; cimetidine may increase levels.

Contraindications:

Carbamazepine and phenytoin may decrease effects; cimetidine may increase levels.

Precautions:

Periodically evaluate hematopoietic and hepatic function during therapy because of reports of neutropenia and disturbed liver function with prolonged therapy; adjust dose in hepatic impairment. Pregnancy: Caution in first trimester of pregnancy. C - Fetal risk

3) Praziquantel (Biltricide):

Increases cell membrane permeability in susceptible worms, resulting in loss of intracellular calcium, massive contractions, and paralysis of musculature. In addition, produces vacuolization and disintegration of schistosome tegument. This is followed by attachment of phagocytes to parasite and death. Isoquinoline derivative that is easily absorbed through GI tract ***(Taylor et al;1988).***

Dosing:

***Adult**:* 40 mg/kg PO qwk.

***Pediatric*:** <4 years: Not established & >4 years: as in adults**.**

Interactions:

Hydantoins may reduce serum concentrations, possibly leading to treatment failures; slows metabolism of benzimidazoles, thus increasing serum levels

Contraindications:

Documented hypersensitivity; ocular cysticercosis

Precautions:

Destruction of parasite within eyes can cause irreparable lesions (ocular cysticercosis should not be treated with praziquantel); minimal increases in liver enzyme levels reported.

Pregnancy: Use in first trimester of pregnancy is discouraged. B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals.

❖ **Monitoring**: Monitor patients for adverse effects of agents every 2 weeks with a CBC count and liver enzyme evaluation for the first 3 months and then every 4 weeks. Monitoring albendazole and mebendazole serum levels is desirable, but few laboratories are capable of performing this measurement. Imaging studies are required for follow-up on the morphologic status of the cyst.

❖ ***Outcome from medical treatment of CE***: Response rates in 1000 treated patients were that 30% had cyst disappearance (cure), 30-50% had a decrease in the size of the cyst (improvement), and 20-40% had no changes. Also, younger adults responded better than older adults.

ii. PAIR in CE:

This technique, performed using either ultrasound or CT guidance, involves aspiration of the contents via a special cannula, followed by injection of a scolicidal agent for at least 15 minutes, and then reaspiration of the cystic contents. This is repeated until the return is clear. The cyst is then filled with isotonic sodium chloride solution ***(Smego et al; 2003).***

Perioperative treatment with a benzimidazole is mandatory (4 d prior to the procedure and 1-3 mo after).

The cysts should be larger than 5 cm in diameter and type I or II according to the *Gharbi ultrasound classification* of liver cysts (ie, type I is purely cystic; type II is purely cystic plus hydatid sand; type III has the membrane undulating in the cystic cavity; and type IV is the peripheral or diffuse distribution of coarse echoes in a complex and heterogeneous mass). PAIR can be performed on type III cysts as long as it is not a honeycomb cyst ***(Gargouri et al; 1990).***

❖ ***Indications:*** Inoperable patients; patients refusing surgery; multiple cysts in segment I, II, and III of the liver; and relapse after surgery or chemotherapy are indications for the PAIR technique.

❖ ***Contraindications:*** Early pregnancy, lung cysts, inaccessible cysts, superficially located cysts (risk of spillage), type II honeycomb cysts, type IV cysts, and cysts communicating with the biliary tree (risk of sclerosing cholangitis from the scolicidal agent) are contraindications for the PAIR technique.

❖ ***Outcome:*** The reduced cost and shorter hospital stay associated with PAIR compared to surgery make it desirable. The risk of spillage and anaphylaxis is considerable, especially in superficially located cysts, and transhepatic puncture is recommended ***(Khoury*** et ***al; 1998).***Sclerosing cholangitis (chemical) and biliary fistulas are other risks.

II) Surgical Care:

❖ ***Indications:*** Large liver cysts with multiple daughter cysts; superficially located single liver cysts that may rupture (traumatically or spontaneously); liver cysts with biliary tree communication or pressure effects on vital organs ; infected cysts; are indications for surgery.

❖ ***Contraindications****:*

General contraindications to surgical procedures (eg, extremes of age, pregnancy, severe preexisting medical conditions); multiple cysts in multiple organs; cysts that are difficult to access; dead cysts; calcified cysts; and very small cysts are contraindications.

❖ ***Choice of surgical technique****:*

Radical surgery (total pericystectomy ***(Elhamel et al; 1990)*** or partial affected organ resection, if possible), conservative surgery (open cystectomy), or simple tube drainage for infected and communicating cysts are choices for surgical technique. The more radical the procedure, the lower the risk of relapses but the higher the risk of complications. Patient care must be individualized accordingly ***(Cirenei et al; 2001).***

Follow-up:

☒ **Further Inpatient Care:**

1. Inpatient care for individuals who have had surgical resection of their hydatid cyst(s) is similar to that for any other surgical procedure on the affected organ.
2. Special consideration must be made for patients with hepatic CE who were found to have biliary communication. These patients must be observed for signs and symptoms of either biliary obstruction or fistula formation. If either of these complications occurs, the patient must be treated by percutaneous or endoscopic stenting of the biliary tree with or without sphincteroplasty.
3. Postoperatively, treatment with benzimidazoles is continued for approximately 1 month.

☒ **Further Outpatient Care:** Outpatient care is directed towards the following end points:

1. ***Chemotherapy:*** Postoperative treatment with benzimidazoles is continued for 1 month in patients with CE who have undergone complete resection or PAIR successfully.

   The treatment is continued for 3-6 months for patients with incompletely resected CE, spillage during surgery or PAIR, and metastatic lesions.

2. ***Laboratory tests****:* Patients on benzimidazoles should have a CBC count and liver enzyme evaluation performed at biweekly intervals for 3 months and then every 4 weeks to monitor for toxicity.

   ELISA or indirect hemagglutination tests are usually performed at 3-, 6-, 12-, and 24-month intervals as screening for recurrence of resected disease or aggravation of existing disease.

3. ***Imaging****:* Ultrasonography and/or CT scan are used in follow-up at the same intervals as the laboratory tests or as clinically indicated.

☒ **Inpatient & Outpatient Medications:**

Antibiotics are used prophylactically for surgery as indicated in patients with a cystobiliary fistula, and for treatment of infected cysts. Benzimidazoles are continued after discharge.

Prognosis:

In CE, prognosis is generally good, with complete cure with total surgical excision without spillage. Spillage occurs in 2-25% of cases (depends on location and surgeon's experience), and the operative mortality rate varies from 0.5-4% for the same reasons ***(Tan et al;1998).***

Complications *(Pedrosa et al; 2000).*:

- All the usual complications related to the surgical procedure and anesthesia.

- Related to the parasite:
  - Recurrence.
  - Metastasis.
  - Infection.
  - Spillage and seeding (secondary echinococcosis).
  - Allergic reaction or anaphylactic shock.
- Related to the medical treatment:
  - Hepatotoxicity.
  - Anemia.
  - Thrombocytopenia.
  - Alopecia.
  - Embryotoxicity.
  - Teratogenicity.
  - Spillage and seeding (secondary echinococcosis).
- Related to PAIR:
  - Hemorrhage.
  - Mechanical damage to other tissue.
  - Infections.
  - Allergic reaction or anaphylactic shock.
  - Persistence of daughter cysts.
  - Sudden intracystic decompression leading to biliary fistulas.
- Related to scolicidal agents - Chemical sclerosing cholangitis ***(Polo et al; 1989).***

Prevention:

Because human infection with *Echinococcus* results from fecal-oral contamination, prevention requires the following steps:

- Education on proper hygiene.
- Proper cleansing of uncooked food and avoidance when possible.
- Dietary regulation of pet dogs (stop the habit of feeding viscera of intermediate hosts, such as sheep, to pet dogs).
- Regulate pet dog activity to prevent ingestion of sheep material.
- Avoidance of unregulated dogs.
- Treatment of pet dogs in endemic areas for intestinal echinococcosis with praziquantel (5 mg/kg) periodically.
- Control of the dog population.
- Regulation of livestock butchering.

Imaging:

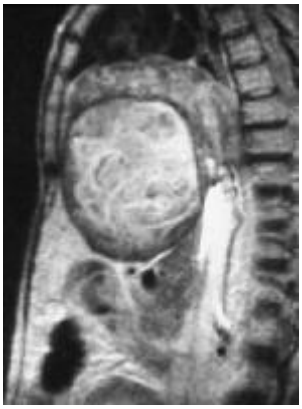


Fig. 30: **Hepatic cysts. Sagittal MRI reconstruction in a patient with a large echinococcal cyst; note daughter cysts in interior.**

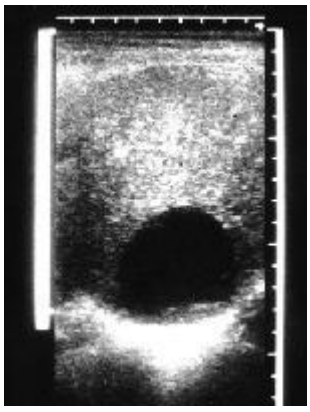


Fig. 31: **Ultrasonographic appearance of echinococcal cysts (Gharbi type I, World Health Organization [WHO] standardized classification CE1).**

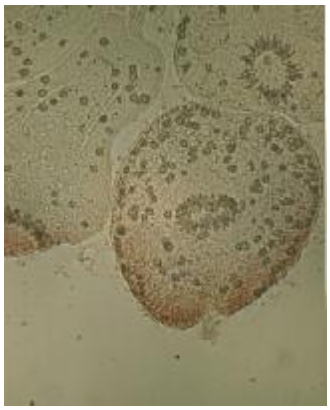


Fig. 32: **Viable scolices (note rostellar hooklets).**

3.Hepatic Abscesses:

Liver abscesses have been recognized since the age of ***Hippocrates***. In 1883, ***Koch*** described the amoebae as a cause of liver abscess. In 1938, ***Ochsner*** and ***Debakey*** published the largest series of pyogenic and amebic liver abscesses in the literature***(Ochsner et al; 1938).*** Since the late 20th century, percutaneous drainage has become a useful therapeutic option***(Gerzof et al;1985& Kandel et al;1984& Rintoul et al;1996& Seeto et al;1996& Stain et al;1991).***

a. Pyogenic Abscesses:

Pyogenic hepatic abscesses are uncommon conditions that present diagnostic and therapeutic challenges to physicians. If left untreated, these lesions are invariably fatal.

Frequency:

The incidence of pyogenic liver abscess has remained unchanged since just prior to the mid-20th century. In the United States, the incidence of pyogenic liver abscess is estimated to be 8-15 cases per 100,000 persons. This figure is considerably higher in countries where health care is not readily available. Studies indicate that the male-to-female ratio is approximately 2:1; the problem occurs most commonly in the fourth to sixth decade of life ***(Branum et al; 1990).***

Etiology:

1. Biliary disease *(Chu et al; 1996)*: Biliary disease accounts for 21-30% of reported cases ***(Kandel et al; 1984& Branum et al; 1990& Gyorffy et al; 1987).***

a. Extrahepatic biliary obstruction leading to ascending cholangitis and abscess formation is the most common cause ***(Branum et***

al;1990& Gyorffy et al;1987) and is usually associated with choledocholithiasis

b. Benign and malignant tumors ***(Rintoul et al; 1996)*** or postsurgical strictures.

c. Biliary enteric anastomoses (choledochoduodenostomy or choledochojejunostomy) have also been associated with a high incidence of liver abscesses ***(Gerzof et al; 1985&Gyorffy et al; 1987)***.

d. Biliary complications (eg, stricture, bile leak) after liver transplantation are also recognized causes of pyogenic liver abscesses.

2. Infection via the portal system (portal pyemia):

a. The infectious process originates within the abdomen and reaches the liver by embolization or seeding of the portal vein. With the liberal use of antibiotics for intra-abdominal infections, portal pyemia is now a less frequent cause of pyogenic liver abscesses but still accounts for 20% of cases ***(Branum et al; 1990)***.

b. Appendicitis and pylephlebitis are the predominant causes.

c. Any source of intra-abdominal abscess, such as acute diverticulitis, inflammatory bowel disease, and perforated hollow viscus, can lead to portal pyemia and hepatic abscesses.

3. Hematogenous (via the hepatic artery):

a. This infectious process results from seeding of bacteria into the liver in cases of systemic bacteremia from bacterial endocarditis, urinary sepsis, or following intravenousdrug abuse ***(Rintoul et al; 1996).***

b. Blunt or penetrating trauma and liver necrosis from inadvertent vascular injury during laparoscopic cholecystectomy are recognized causes of liver abscess ***(Branum et al; 1990)***.

c. Transarterial embolization and cryoablation of liver masses are now recognized as new etiologies of pyogenic abscesses ***(Rockey et al; 1999).***

4. Cryptogenic: No cause is found in approximately half of the cases. However, the incidence is increased in patients with diabetes or metastatic cancer. Patients with repeated cryptogenic liver abscesses should undergo biliary and gastrointestinal evaluation ***(Branum et al;1990)***.

Pathophysiology:

Pyogenic bacteria can gain access to the liver by direct extension from contiguous organs or through the portal vein or hepatic artery. Hepatic clearance of bacteria via the portal system appears to be a normal phenomenon in healthy individuals; however, organism proliferation, tissue invasion, and abscess formation can occur with biliary obstruction, poor perfusion, or microembolization.

Microbiology:

The organisms isolated most often are included below. Most abscesses contain more than 1 organism and frequently are of biliary or enteric origin. Blood culture results are positive in 33-65% of cases ***(Branum et al;1990)***, with positive results from abscess cultures reported in 73-100% of series***(Branum et al;1990& Gyorffy et al;1987)***.

Escherichia coli is the most common organism isolated in western series, while Klebsiella pneumoniae has recently emerged as a common

isolate in patients with diabetes in Taiwan***(Tsai et al;2008& Pastagia et al;2008& Cheng et al;2008).***

The most common microorganisms isolated from blood and abscess cultures are as follows***(Branum et al;1990&Gyorffy et al;1987):***

- E coli - 33%
- K pneumoniae - 18%
- Bacteroides species - 24%
- Streptococcal species - 37%
- Microaerophilic streptococci - 12%

Presentation:

The clinical presentation of liver abscess is insidious; many patients have symptoms for weeks prior to presentation. Fever and right upper quadrant pain are the most common complaints ***(Gyorffy et al;1987& Giorgio* et al;2006)**

I. Symptoms:

- Pain is reported in as many as 80% of patients and may be associated with pleuritic chest pain(9-24%) or right shoulder pain. Symptoms are often misdiagnosed as acute cholecystitis.
- Fever occurs in 87-100% of patients and is usually associated with chills and malaise ***(Gyorffy et al;1987).***
- Anorexia (38-80%), weight loss (25-68%),Cough (11-28%) and mental confusion are also common symptoms.

II. Signs:

- Right upper quadrent tenderness (41-72%).

- Hepatomegaly (51-92%), liver mass (17-18%), and jaundice (23-43%) are also common.
- Occasionally, patients may present with rales, pleural effusion, friction rub, or pulmonary consolidation (11-48%).
- Rarely, patients are admitted with sepsis and peritonitis from intraperitoneal rupture of the abscess.

Laboratory Studies:

1. ***Complete blood cell count***:
    a. Anemia is observed in 50-80% of patients ***(Branum et al; 1990&Gyorffy et al; 1987).***
    b. Leukocytosis of more than 10,000/mm ***(Kandel et al; 1984)*** in 75-96% of patients ***(Branum et al; 1990&Gyorffy et al; 1987).***
    c. Bands of more than 10% are observed in 40% of patients.
2. ***Erythrocyte sedimentation rate*** (ESR) is commonly elevated.
3. ***Prothrombin time (Chu et al; 1996)***: elevated in 71-87% of patients.
4. ***Liver function tests***:
    a. An elevated alkaline phosphatase level ***(Kandel et al; 1984)*** in 95-100% of patients ***(Branum et al; 1990&Gyorffy et al; 1987).***
    b. An elevated serum aspartate aminotransferase level, an elevated serum alanine aminotransferase level, or elevated levels of both are observed in 48-60% of patients.
    c. An elevated bilirubin level ***(Chu et al; 1996)*** is observed in 28-73% of patients ***(Branum et al; 1990&Gyorffy et al; 1987).***
    d. A decreased albumin level (<3 g/dL) and increased globulin value (>3 g/dL) are frequently observed.

Imaging Studies:

Chest and abdominal radiographs are nonspecific, but they are frequently obtained at the initial evaluation.

I. <u>Chest radiography</u>:

- Findings are abnormal in approximately half the patients.
- Nonspecific findings may include an elevated right hemidiaphragm, subdiaphragmatic air-fluid level, pneumonitis, consolidation, and pleural effusion.

II. *<u>Abdominal radiograph</u>*:

- If gas-forming organisms are present, the abdominal x-ray film might show evidence of intrahepatic air, portal venous gas, air-fluid levels, or air in the biliary tree.

III. <u>Radionucleotide sulfur colloid scan</u>:

- The role of the radionucleotide scan has been completely replaced by CT scan and ultrasonography.
- Findings can help reliably detect masses larger than 2 cm.
- The sensitivity of the findings ranges from 50-80%; however, they lack specificity.

IV.* <u>Ultrasonography</u>*(Seeto et al;1996& Gyorffy et al;1987& Hashimoto et al;1995& Benedetti et al; 2008).

- Real-time ultrasonography findings are 80-100% sensitive ***(Rubinson et al; 1980&Ferrucci et al; 1981).***A round or oval hypoechoic mass is consistent with pyogenic abscess.

V.* <u>CT scanning</u> *(Seeto et al; 1996& Gyorffy et al; 1987& Hashimoto et al; 1995& Benedetti et al; 2008).

- CT scanning has become the imaging study of choice for detecting liver lesions ***(Rubinson et al; 1980&Ferrucci et al; 1981).***
- Pyogenic liver abscesses are not enhanced on images after intravenous contrast administration.
- Triphasic CT scanning with arterial and portal venous phases helps to define the proximity of the abscess to the major branches of the portal and hepatic veins
- Findings have sensitivity similar to that of ultrasonography, but they lack specificity.

Diagnostic Procedures:

Diagnostic aspiration is performed under ultrasonographic or CT guidance ***(Gyorffy et al; 1987&Hashimoto et al; 1995)*** and is usually followed by drainage catheter placement. The aspirate is sent for culture and cytology.

Treatment:

The most dramatic change in the treatment of pyogenic liver abscess has been the emergence of CT-guided drainage. Prior to this modality, open surgical drainage was the treatment most often employed, with mortality rates as high as 70%. If the abscess is multiloculated, multiple catheters might be needed to achieve adequate drainage.

The current accepted approach includes 3 steps, as follows:

- Initiation of antibiotic therapy.
- Diagnostic aspiration and drainage of the abscess.
- Surgical drainage in selected patients ***(Stain et al; 1991& Hope et al; 2008).***

1. Antibiotic therapy ***(Kandel et al; 1984&Rintoul et al; 1996& Seeto et al; 1996& Stain et al; 1991& Hope et al; 2008):*** Diagnostic aspiration should be performed as soon as possible. The antimicrobial agent should provide adequate coverage against aerobic gram-negative bacilli, microaerophilic streptococci, and anaerobic organisms, including Bacteroides fragilis.

Usually, a combination of 2 or more antibiotics is used. Metronidazole and clindamycin have wide anaerobic coverage and provide excellent penetration into the abscess cavity. A third-generation cephalosporin or an aminoglycoside provides excellent coverage against most gram-negative organisms. Fluoroquinolones are an acceptable alternative in patients who are allergic to penicillin. This modality has been shown to be effective in patients with unilocular abscesses that are less than 3 cm in size ***(Chung et al; 2007).***

2. Percutaneous drainage*: (Gerzof et al; 1985 Kandel et al; 1984& Rintoul et al ;1996& Seeto et al ;1996& Stain et al ;1991& Hope et al ;2008):* Diagnostic aspiration should be performed as soon as the diagnosis is made. It can be performed under ultrasonographic ***(Giorgio et al; 2006& Men et al; 2002)*** (if small or superficial) or CT guidance and is usually followed by placement of a drainage catheter.

Multiple abscesses necessitate CT guided drainage ***(Giorgio et al; 2006).*** Once positioned, the catheter should be irrigated with isotonic sodium chloride solution and placed to allow gravity drainage.

The drain is removed when the abscess cavity collapses, as confirmed on CT scan images. Presence of ascites and proximity to vital structures are contraindications to percutaneous drainage. Coagulopathy can be corrected with transfusion of fresh frozen plasma prior to drainage.

The success rate of percutaneous drainage ranges from 80-87% ***(Gerzof et al; 1985).*** Consider percutaneous drainage to have failed if no improvement occurs, if the condition worsens within 72 hours of drainage, or if the abscess recurs despite adequate initial drainage. Percutaneous drainage failure can be treated by either inserting a second catheter or performing open surgical drainage.

* ***Complications of percutaneous drainage***: include perforation of adjacent abdominal organs, pneumothorax, hemorrhage, and leakage of the abscess cavity into the peritoneum.
* ***Contraindication of percutaneous drainage***: Immunocompromised patients with multiple diffuse microabscesses are not candidates for either percutaneous or open surgical drainage and are best treated with high-dose antibiotics. Such patients have highest mortality rate.

3. Surgical Therapy:

Surgical drainage was once considered to be the criterion standard in treating liver abscesses. Currently, surgical drainage is indicated in:

Indications:

Presently, most liver abscesses are treated with antibiotics and catheter drainage under ultrasonographic or computed tomography (CT) scan guidance. The indications for surgical drainage are as follows:

- Abscess not amenable to percutaneous drainage secondary to location
- Coexistence of intra-abdominal disease that requires operative management
- Failure of antibiotic therapy.
- Failure of percutaneous aspirationor drainage ***(Yanaga et al; 1994& Siu et al; 1997).***

- Abscesses larger than 5 cm ***(Chung et al; 2007).***
- Concominant biliary/intra-abdominal disease ***(Chung et al; 2007).***

The presence of peritoneal signs in a patient with pyogenic liver abscess mandates emergent laparotomy because free rupture of the abscess into the peritoneal cavity may have occurred.

Liver resection should be considered, when the following are present: Liver carbuncle, hepatolithiasis, suspicious lesion that would require control of sepsis prior to surgical procedure ***(Gyorffy et al; 1987).***

Contraindications:

Relative contraindications to surgery include the following:

- Multiple abscesses.
- Polymicrobial infection.
- Presence of associated malignancy or immunosuppressive disease.
- Coexistence of other multiple and/or complicated medical problems or conditions.

Complications:

The complications of liver abscess result from rupture of the abscess into adjacent organs or body cavities. These include pleuropulmonary and intra-abdominal types.

- ***Pleuropulmonary complications*** are the most common and have been reported in 15-20% of early series. These include pleurisy and pleural effusion, empyema, and broncho-hepatic fistula ***(Ochsner et al; 1938).***
- ***Intra-abdominal complications*** are also common. These complications include subphrenic abscess and rupture into the peritoneal cavity, stomach, colon, vena cava, or kidney. A large

abscess compressing the inferior vena cava and the hepatic veins may result in Budd-Chiari syndrome.Rupture into the pericardium or brain abscess from hematogenous spread is rare.

Outcome and Prognosis:

Untreated, pyogenic liver abscess is associated with 100% mortality. Early series reported a mortality rate of greater than 80%. With early diagnosis, appropriate drainage, and long-term antibiotic therapy, the prognosis has improved markedly ***(Chu et al; 1996)***, with mortality rates in the range of 15-20% ***(Gyorffy et al; 1987&Hashimoto et al; 1995)***.

Poor prognostic factors are as follows:

- Age older than 70 years
- Multiple abscesses
- Polymicrobial infection
- Presence of associated malignancy or immunosuppressive disease ***(Seeto et al; 1996& Branum et al; 1990).***
- Evidence of sepsis ***(Seeto et al; 1996&Gyorffy et al; 1987& Bowers et al; 1990& Chou et al; 1994& Wang et al; 2004).***

Future and Controversies

Because of practitioners' increased experience in the laparoscopic approach to liver lesions, laparoscopic drainage of pyogenic hepatic abscesses is being performed safely, and the time required to carry out the procedure has been reduced ***(Yanaga et al; 1994&Siu et al; 1997& Robles et al; 1994).***

The laparoscopic approach eliminates access trauma and can help detect predisposing pathology.

Intraoperative laparoscopic ultrasonography can accurately detect the location of the abscess to allow for drainage under ultrasonographic guidance. It has thus far been shown as a relatively safe alternative,***(Robles et al;1994)*** and as experience with the use of the laparoscope increases, its application in the management of hepatic abscess continues to evolve ***(Rockey et al;1999&Yanaga et al;1994).***

Imaging:

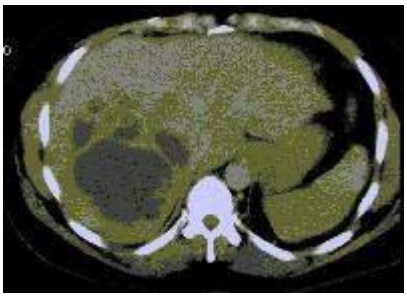


Fig. 33: **Computed tomography scan of liver abscess revealing a large, septated abscess of the right hepatic lobe. Abscess was successfully treated with percutaneous drainage and antimicrobial therapy. Image courtesy of *Michelle V. Lisgaris, MD*.**

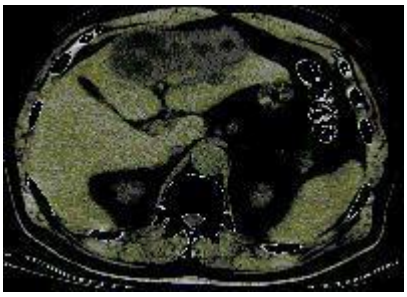


Fig. 34: **Computed tomography scan of liver abscess revealing a large anterior abscess involving the left hepatic lobe. Abscess was successfully treated with percutaneous drainage and antimicrobial therapy*. Image courtesy of Michelle*.**

b. Amebic abscess:

Amebic liver abscess is the most frequent extraintestinal manifestation of *Entamoeba histolytica* infection. This infection is caused by the protozoa *E histolytica*, which ascends the portal venous system. Amebic liver abscess is an important cause of space-occupying lesions of the liver, mainly in developing countries. Prompt recognition and appropriate treatment of amebic liver abscess lead to improved morbidity and mortality rates.

Pathophysiology

E histolytica exists in 2 forms. The cyst stage is the infective form, and the trophozoite stage causes invasive disease. People who chronically carry *E histolytica* shed cysts in their feces; these cysts are transmitted primarily by food and water contamination. Rare cases of transmission via oral and anal sex or direct colonic inoculation through colonic irrigation devices have occurred.

Cysts are resistant to gastric acid, but the wall is broken down by trypsin in the small intestine. Trophozoites are released and colonize the cecum. To initiate symptomatic infection, *E histolytica* trophozoites present in the lumen must adhere to the underlying mucosa and penetrate the mucosal layer.

Liver involvement occurs following invasion of *E histolytica* into mesenteric venules. Amebae then enter the portal circulation and travel to the liver where they typically form large abscesses. The Gal/GalNAc lectin is an adhesion protein complex that sustains tissue invasion ***(Blazquez et al; 2007).***

The abscess contains acellular proteinaceous debris, which is thought to be a consequence of induced apoptosis ***(Stanley SL Jr. 2003)*** and is surrounded by a rim of amebic trophozoites invading the tissue.

The right lobe of the liver is more commonly affected than the left lobe. This has been attributed to the fact that the right lobe portal laminar blood flow is supplied predominantly by the superior mesenteric vein, whereas the left lobe portal blood flow is supplied by the splenic vein.

Frequency:

Amebic liver abscess is rare and is currently seen almost exclusively in immigrants or travelers. In 1994, 2,983 cases of amebiasis were reported to the Centers for Disease Control (CDC). The disease was removed from the National Notifiable Diseases Surveillance System in 1995. An estimated 4% of patients with amebic colitis develop an amebic liver abscess.

An estimated 10% of the population is infected with *Entamoeba dispar*. Previously thought to be a nonpathogenic strain of *E histolytica*, this type of amoeba does not produce clinical symptoms even in the immunocompromised host.

International:

Worldwide, approximately 40-50 million people are infected annually, with the majority of infections occurring in developing countries. The prevalence of infection is higher than 5-10% in endemic areas ***(Blessmann et al; 2003)*** and sometimes as high as 55% ***(Haque et al; 2002).***

The highest prevalence is found in developing countries in the tropics, particularly in Mexico, India, Central and South America, and tropical areas of Asia and Africa.

Mortality/Morbidity:

Infection with *E histolytica* ranks second worldwide among parasitic causes of death, following malaria.

- Annually, 40,000-100,000 deaths are caused by infection with *E histolytica*.
- Per year, a 10% risk of developing symptomatic invasive amebiasis exists after the acquisition of a pathogenic strain.

Race:

All races can be affected by amebic liver abscess. Risk factors for infection include travel or residence in endemic areas.

Sex:

Amebic liver abscess is marked by a 7-12 times higher incidence in males than in females despite an equal sex distribution of noninvasive colonic amebic disease among adults ***(Acuna-Soto et al; 2000).***

However, no sexual preponderance exists among children.

Age:

Peak incidence of amebic liver abscess occurs in people in their third, fourth, and fifth decades, although it can occur in any age group.

Clinical findings:

History:

The signs and symptoms of amebic liver abscess often are nonspecific, resembling those of pyogenic liver abscess or other febrile diseases ***(Hoffner et al; 1998& Hughes et al; 2000& Ravdin JI. 1995& Ravdin et al; 2005).***

- **Time of onset:**
    - Patients with amebic liver abscess usually present acutely (duration of symptoms <14 d), with the most frequent complaints being fever and abdominal pain. This presentation is characteristic of younger patients.

- The subacute presentation is characterized by weight loss, and in less than half the cases, abdominal pain and fever is present.

- **Abdominal pain:**
  - Abdominal pain is the most common element in the history and is present in 90-93% of patients.
  - The pain most frequently is located in the right upper quadrant (54-67%) and may radiate to the right shoulder or scapular area.
  - Pain increases with coughing, walking, and deep breathing, and it increases when patients rest on their right side.
  - The pain usually is constant, dull, and aching.
- **Constitutional symptoms:**
  - Fever is present in 87-100% of cases.
  - Rigors are present in 36-69% of cases.
  - Nausea and vomiting are present in 32-85% of cases.
  - Weight loss is present in 33-64% of cases.
- **Diarrhea**:
  - Diarrhea is present in less than one third of patients at the time of diagnosis.
  - Some patients describe a history of having had dysentery within the previous few months.
  - Bloody diarrhea is present in 7% of cases.
- **Pulmonary symptoms:**
  - Pulmonary symptoms are present in 18-26% of cases.
  - The most frequent symptoms are cough and chest pain, which may represent a sign of secondary pulmonary involvement by abscess rupture in the pleural cavity.

- When coughing produces an odorless brown substance similar to anchovy paste, a bronchopleural fistula has developed ***(Mbaye et al; 1998).***

- **Recent travel to endemic areas:**
  - Onset of symptoms usually occurs within 8-12 weeks from the date of travel.
  - In 95% of cases, onset occurs within 5 months of returning from travel to an endemic area.
  - A remote travel history of as many as 12 years has been reported.

Physical findings:

- Fever is the most common sign and is found in as many as 99% of cases.
- Hepatomegaly is present in some cases.
  - The frequency varies widely in different series published, reporting as high as 63% in one series and as low as 18% in another.
  - Hepatomegaly with pain upon palpation is one of the most important signs of amebic liver abscess.
  - Point tenderness over the liver, below the ribs, or in the intercostal spaces is a typical finding.
- Abdominal tenderness:
  - In 55-75% of cases, abdominal tenderness is located in the right upper abdominal quadrant.
  - When the abscess is located in the left lobe (28% of cases), epigastric tenderness is noted.
- Pulmonary abnormalities:

- Pulmonary abnormalities are present in 20-45% of cases and consist of dullness and rales at the right lung base and nonproductive cough.
- Breath sounds over the right lung base may be diminished.
- Pleural rub may be audible.

- Jaundice (<10% of cases) mostly occurs in complicated cases with multiple abscesses or a large abscess compressing the biliary tract.
- ***Signs of complications***
  - Signs of peritoneal irritation, such as rebound tenderness, guarding, and absence of bowel sounds, are present when the abscess ruptures in the peritoneal cavity. Peritonitis occurs in 2-7% of cases.
  - Pericardial friction rub can be audible when the abscess extends into the pericardium. This sign is associated with very high mortality.
  - Signs of pleural effusion are present when the abscess ruptures in the pleural cavity.

Causes:

The following are the risk factors associated with amebic liver abscess:

- Immigrants from endemic areas.
- Institutionalized persons, especially people with mental retardation.
- Crowding and poor hygiene.
- Men who have sex with men (secondary to sexually acquired amebic colitis).
- Presence of immunosuppression (eg, HIV infection, malnutrition with hypoalbuminemia, alcohol abuse, chronic infections, posttraumatic splenectomy, steroid use).

Differential Diagnoses:

- Biliary diseases.
- Hydated cyst.
- Cholycystitis.
- Liver abcess.
- Malaria.
- Echinococcus hydatid cysts.
- Hepatocellular adenoma.

Other Problems to Be Considered:

- Hepatitis.
- Pneumonia.
- Pulmonary disease**.**

Laboratory Studies:

- **Hematology:**
  - Approximately three fourths of patients with an amebic liver abscess have leukocytosis. This most likely will appear if symptoms are acute or complications have developed.
  - Eosinophilia is rare.
  - Anemia may be present, but the cause usually is multifactorial.
- **Chemistry:**
  - Hyperbilirubinemia is present in only a small proportion of cases.
  - In acute liver abscess, the aspartate aminotransferase (AST) levels are high.
  - In chronic liver abscess, the alkaline phosphatase level tends to be elevated and the AST level tends to be within normal limits. Overall, the alkaline phosphatase level is elevated in about 70% of cases of amebic liver abscess.

- Similar CBC count and liver test abnormalities are found in patients with pyogenic liver abscesses and are not specific.

- **Stool examination:**
  - The role of microscopic stool examination is limited. Less than 30-40% of patients with amebic liver abscess have concomitant intestinal amebiasis, and 10% of the population is infected with the nonpathogenic strain of *E dispar*. Hence, the microscopic examination of the stool for the identification of cysts is of little value. If positive, it may suggest the diagnosis.
  - Fecal findings suggestive of amebic colitis include a positive test for heme, a paucity of neutrophils, and the presence of Charcot-Leyden crystal protein. The stool examination is still of value if the serologic and antigen identification tests are not available.
- **Stool antigen detection:**
  - Stool antigen detection facilitates early diagnosis before an antibody response occurs (<7 d) and differentiates pathogenic from nonpathogenic *Entamoeba* infection. The primary drawbacks are the requirement for fresh, unpreserved stool specimens ***(Tanyuksel et al; 2003)*** and the lack of intestinal amebiasis in as many as 60% of patients with amebic liver abscess.
  - Stool antigen detection kits based on enzyme immunoassay (EIA) are most common and still quite sensitive compared to polymerase chain reaction (PCR)-based methods***(Solaymani et al; 2006).***
  - The PCR stool test shows high sensitivity for detecting *E histolytica* and for distinguishing nonpathogenic amoebas ***(Hamzah et al; 2006& Khairnar et al; 2007& Roy et al; 2005).***
  - Stool culture for amoeba is sensitive but has limited availability ***(Qvarnstrom et al; 2005)***.

- **Serologic testing:**

Serologic testing is the most widely used method of diagnosis for amebic liver abscess. In general, the test result should be positive, even in cases when the result of the stool test is negative (only extraintestinal disease).

  - EIA test detects antibodies specific for *E histolytica* in approximately 95% of patients with extraintestinal amebiasis, in 70% of patients with active intestinal infection, and in 10% of persons who are asymptomatic cyst passers ***(Knobloch et al; 1983& Restrepo et al; 1996).***
  - The EIA serology findings revert to negative in 6-12 months following eradication of infection. Even in highly endemic areas, fewer than 10% of patients who are asymptomatic have positive amebic serology findings.
  - Initial negative test results may appear in as many as 10% of patients with amebic liver abscess. Under these circumstances, order repeat serology testing in 1 week. This test result will usually be positive.

- **Serum antigen detection:**
  - *E histolytica* galactose lectin antigen is detectable by enzyme-linked immunosorbent assay (ELISA) in at least 75% of serum samples obtained from patients with amebic liver abscess. Studies reported an antigen seropositivity of 96% with a reversal rate of 82% after 1 week of treatment with metronidazole. This test may be useful for patients who present acutely, before an antibody response occurs. ***(Tanyuksel et al; 2003).***
  - Rapid antigen and antibody tests are currently being evaluated and seem very promising ***(Leo et al; 2006).***

Imaging Studies:

- **Ultrasonography** is the preferable initial diagnostic test. It is rapid, inexpensive, and is only slightly less sensitive than CT scan (75-80% sensitivity vs 88-95% for CT scan).
    - Ultrasonography simultaneously evaluates the gallbladder and avoids radiation exposure.
    - As opposed to scanning with technetium-99m, sonography often can distinguish an abscess from a tumor or other solid focal lesion.
    - The lesions tend to be round or oval, with well-defined margins, and hypoechoic.
- **CT scan** is sensitive but the findings are not specific.
    - The abscess typically appears low density with smooth margins and a contrast-enhancing peripheral rim.
    - The use of injected contrast may differentiate hepatic abscesses from vascular tumors.
- **MRI** is sensitive, but the findings are not specific. This test provides information comparable with less expensive imaging procedures.
- **Technetium-99m liver scanning** is useful for differentiating an amebic liver abscess from a pyogenic abscess; however, it is not used as a first-line test.
    - Because amebic liver abscesses do not contain leukocytes, they appear as cold lesions on hepatic nuclear scanning, with a typical hot halo or a rim of radioactivity surrounding the abscess.
    - In contrast, pyogenic liver abscesses contain leukocytes and, therefore, typically appear as hot lesions on nuclear scanning.

- **Gallium scanning** is helpful in differentiating pyogenic abscess (similar to technetium-99m nuclear hepatic scanning) but requires delayed images, which makes the test less helpful.
- **Hepatic angiography** is only useful to differentiate liver abscesses from vascular lesions.
- **Plain chest** or **abdominal films** may show elevation and limitation of motion of the right diaphragm, basilar atelectasis, and right pleural effusion or gas within the abscess cavity.
- None of the imaging tests can definitely differentiate a pyogenic liver abscess, an amebic abscess, or malignant disease. Clinical, epidemiological, and serological correlation is needed for diagnosis.

Treatment:

I) Medical Care:

Most uncomplicated amebic liver abscesses can be treated successfully with amebicidal drug therapy alone. Use tissue amebicides to eradicate the invasive trophozoite forms in the liver. After completion of treatment with tissue amebicides, administer luminal amebicides for eradication of the asymptomatic colonization state. Failure to use luminal agents can lead to relapse of infection in approximately 10% of patients.

In general, ***metronidazole***, ***tinidazole***, ***emetine***, and ***dehydroemetine*** are active in invaded tissues; ***chloroquine*** is active only in the liver; ***tetracycline*** acts on the bowel wall; and ***diloxanide furoate***, ***paromomycin***, and ***iodoquinol*** are luminal agents only.

❖ **Metronidazole** remains the drug of choice for amebic liver abscess. Metronidazole enters the protozoa by passive diffusion and is converted to reactive cytotoxic nitroradicals by reduced ferredoxin or flavodoxin.

❖ **Tinidazole**, another nitroimidazole closely related to metronidazole, was approved for the treatment of amebic liver abscess and invasive amebiasis. Tinidazole is well tolerated by patients. Tinidazole may be administered once daily and appears to be at least as effective as metronidazole, with a clinical cure rate of more than 90%.

- Metronidazole, 750 mg 3 times a day orally for 10 days, was reported to be curative in 90% of patients with amebic liver abscess. The drug also is available for intravenous administration for those patients who are unable to take medication by the oral route.
- Resolution of symptoms is fairly rapid and is observed within 3 days in most of the patients in the United States. In endemic areas outside the United States, it takes relatively longer to resolve symptoms because the abscesses are quite large or multiple by the time patients seek medical attention.
- In vivo resistance to metronidazole by *E histolytica* has not been reported. Nevertheless, in vitro studies have shown an association between metronidazole resistance and decreased expression of ferredoxin 1 and flavodoxin and increased expression of iron-containing superoxide dismutase and peroxiredoxin in *E histolytica*.
- ***Adverse effects*** of metronidazole include nausea, headache, and metallic taste. Abdominal cramps, vomiting, diarrhea, and dizziness also may occur. Dark urine may occur from a metabolite of the drug.
- No randomized controlled trials exist that demonstrate the benefits of combination therapy over monotherapy.

Other closely related amebicidal agents, such as **secnidazole** or **ornidazole**, can be substituted in appropriate dosages.

- **Chloroquine phosphate** may be substituted or added in the event of failure of resolution of clinical symptoms with metronidazole or another nitroimidazole within 5 days or intolerance to metronidazole or a nitroimidazole. Chloroquine has the disadvantage of being associated with higher relapse rates than nitroimidazoles. ***Adverse effects*** include gastrointestinal upset, headache, dizziness, and blurred vision. Retinopathy does not occur at the dose used for amebic liver abscess.
- **Emetine** or **dehydroemetine** has a direct lethal action on the trophozoites of *E histolytica*. These agents are very toxic and, therefore, should be used only as a second-line therapy. Their toxicity includes cardiac arrhythmias, precordial pain, muscle weakness, vomiting, and diarrhea. **Dehydroemetine** is less toxic than emetine.

Administer a luminal amebicidal agent to eradicate the intestinal carriage after the amebic liver abscess has been treated with one of the above tissue amebicides. Failure to use luminal agents can lead to relapse of infection in approximately 10% of patients.

Luminal agents with proven efficacy include:

- **Diloxanide furoate** is free of major adverse effects. The most common adverse effect is flatulence and occasional gastrointestinal upset.
- **Iodoquinol** (diiodohydroxyquin) rarely causes abdominal pain, diarrhea, or rash. A structurally related diiodohydroxyquin caused subacute myelopticoneuropathy and is obsolete now.
- Although **paromomycin** may occasionally cause nausea, abdominal cramps, or diarrhea, it is the preferred luminal amebicidal.

II) Surgical Care:

- Consider therapeutic aspiration of amebic liver abscess in the following situations: (1) high risk of abscess rupture, as defined by cavity size greater than 5 cm; (2) left lobe liver abscess, which is associated with higher mortality and frequency of peritoneal leak or rupture into the pericardium; (3) failure to observe a clinical medical response to therapy within 5-7 days; and (4) cannot differentiate from a pyogenic abscess.
- The following are predictive of the need for aspiration: (1) age older than 55 years, (2) abscess greater than 5 cm in diameter, and (3) failure of medical therapy after 7 days***(Khan et al; 2008).***
- In endemic areas, because of the late presentation and the existence of multiple abscesses, as many as 50% of patients may require aspiration ***(Khanna et al; 2005).***
- Routine needle aspiration offers only minimal benefit over medical care alone for uncomplicated amebic liver abscess and, unless one of the above indications exists, should be avoided ***(Blessmann et al; 2003).*** Prompt medical care decreases the need for aspiration ***(Maltz et al; 1991).***

Procedures:

Imaging guided needle aspiration & catheter drainage are the procedures of choice. Generally, surgical drainage is not necessary and should be avoided; however, consider open surgical drainage when the abscess is inaccessible to needle drainage , rupture of the abscess is thought to be imminent, differentiation between amebic abscess and pyogenic abscess is critical, or no response to antiprotozoal therapy occurs in 5-7 days.

- *Simple needle aspiration* is less invasive, is less expensive, and has the advantage of being able to drain multiple abscesses in the same

session. Simple needle aspiration avoids problems related to catheter care.

- Although *catheter drainage* may be more effective than needle aspiration, in a study by ***Rajak*** et al***, (Rajak et al; 1998),*** the average time for clinical improvement, mean hospital stay, and time to resolution were similar among the patients who were successfully treated in the 2 treatment groups.
- Aspiration may be performed under *CT* scan or *sonographic* guidance. Send the collected specimen for *Gram stain* and *cultures*.Amebas rarely are recovered from the aspirate (15%), and often they are present only in the peripheral parts of the abscess, invading and destroying adjacent tissue.
- Amebic liver abscesses only rarely yield positive bacterial cultures following secondary bacterial infection of the abscess cavity.
- Detecting *E histolytica* antigen in the aspirate is possible and is accomplished as previously described for stool specimens. It is highly specific. The sensitivity was only 20% using ELISA, but newer PCR-based assays have a sensitivity of 83% and a specificity of 100%. ***(Khan et al; 2006).*** However, currently, PCR-based detection is not widely available.
- Many possible ***complications*** are associated with aspiration of the abscess. The most common complications are infection and bleeding. Other complications include amebic peritonitis or inadvertent puncture of an echinococcal cyst.

Histologic Findings:

The liver involvement in amebiasis consists of necrotic abscesses and periportal inflammation. The abscess contains acellular proteinaceous debris and is surrounded by a rim of amebic trophozoites invading tissue.

The abscess contains a chocolate-colored fluid that resembles anchovy paste and consists predominantly of necrotic hepatocytes. Triangular areas of hepatic necrosis, possibly due to ischemia from amebic obstruction of portal vessels, have been observed. *E histolytica* can also induce hepatocyte and neutrophilic apoptosis.

Diet:

No specific diet change or modification is required. However, discuss food hygiene with patients because amebiasis is associated with suboptimal personal or food hygiene.

Activity:

- No restriction of activity is needed, except during the first few days of acute illness with pain.
- If emetine or dehydroemetine is used, the patient should remain sedentary for approximately 4 weeks after completing therapy because of their toxicity.

Follow-up:

Further Outpatient Care:

- Follow-up ultrasonography or CT scan is unnecessary after resolution of symptoms and signs because the radiological resolution may take several months to years.
- Luminal amebicides fail to eradicate the luminal forms of *E histolytica* in approximately 10-15% of patients treated with these agents; therefore, a follow-up stool examination is recommended after completion of therapy. A second course of a luminal amebicide is required in a few weeks if the first course fails to eradicate the intestinal carriage.

Prevention:

1. Control of amebiasis can be achieved by exercising proper sanitary measures and avoiding fecally contaminated food and water.
   - ❖ Regular examination of food handlers and thorough investigation of diarrheal episodes may identify the source of infection in some communities.
   - ❖ Vegetables must be cleaned with a strong detergent soap and soaked in acetic acid or vinegar for approximately 15 minutes to eradicate the cyst forms.
   - ❖ Boiling is the only effective means of eradicating the cysts in water.
   - ❖ Travelers to areas with suboptimal sanitation and hygiene should eat only cooked foods or fruits peeled by themselves and should avoid drinking local water, including ice cubes frequently used for cocktails. Notably, many types of bottled water in developing countries are not properly disinfected.
2. No prophylactic vaccine currently is available for amebiasis, but efforts to better define antigenic candidates are encouraging**.** ***(Stanley et al; 2006 & Snow et al; 2006).***
   - ❖ A serine-rich *E histolytica* protein (SREHP) has been expressed in avirulent vaccine strains of *Salmonella species*.
   - ❖ *E histolytica* galactose/*N* -acetyl-D-galactosamine (Gal/GalNAc)***(Houpt et al 2004)*** and synthetic enhanced intranasal lectin-based amebiasis subunits ***(Abd Alla et al; 2007)*** have been extensively studied as attractive candidates for vaccine development.
   - ❖ Gal-inhibitable lectin shows promise in animal studies**.** ***(Ivory et al; 2007).***

Complications:

1. Pleuropulmonary infection is the most common complication. Mechanisms of infection include development of a sympathetic serous effusion; rupture of a liver abscess into the chest cavity, leading to empyema; or hematogenous spread, resulting in parenchymal infection.
2. Bronchopleural fistula may occur in rare instances when patients expectorate a substance that resembles anchovy paste. Trophozoites may be demonstrated in the fluid.
3. Cardiac involvement results following the rupture of an abscess involving the left lobe of the liver. It usually is associated with very high mortality.
4. Intraperitoneal rupture occurs in 2-7% of patients. Left lobe abscesses are more likely to progress to rupture because of their later clinical presentation.
5. Bacterial superinfection can occur.
6. Rupture into peritoneal organs and mediastinum can occur.
7. Cases of hepatic artery pseudoaneurysm have been reported.

Prognosis:

- In most cases, rapid clinical improvement is observed in less than 1 week with antiamebic drug therapy alone. Radiological resolution lags behind the resolution of clinical symptoms. The average time to radiological resolution is approximately 12 months, with a range of 3 months to more than 10 years.
- Death occurs in approximately 5% of persons having extraintestinal infection, including liver abscess. Rupture into the peritoneal cavity and the pericardium are responsible for most deaths.

Imaging:

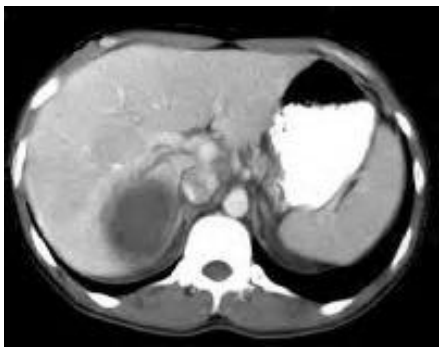


Fig. 35: **CT scan of the abdomen with IV and oral contrast is shown. Note the thick-walled cavity with low attenuation center and contrast-enhanced periphery.**

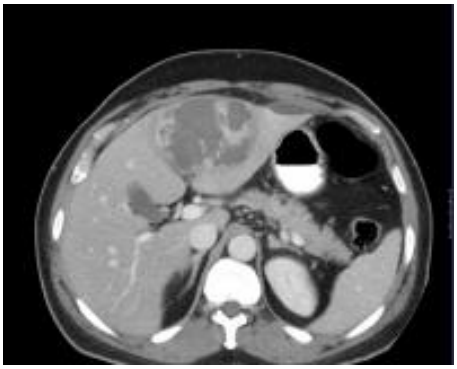


Fig.36: **CT scan of the abdomen with contrast showing large amebic abscess with multiloculated appearance and atypical left liver lobe location. CT scan cannot differentiate amebic liver abscess from pyogenic liver abscess.**

4. Fibropolycystic Liver Disease

Fibropolycystic liver disease encompasses a spectrum of related lesions of the liver and biliary tract that are caused by abnormal embryologic development of the ductal plates ***(Sherlock S.1999&Ishak et al; 2001&Summerfield et al; 1986&Desmet VJ. 1992).*** These lesions; **(***congenital hepatic fibrosis***,** *biliary hamartomas***,** *Caroli disease***,** *choledochal cysts***)** can be clinically silent or can cause signs and symptoms such as cholangitis, portal hypertension, gastrointestinal bleeding, infections, and space-occupying masses.

The different types of fibropolycystic liver disease demonstrate characteristic findings at computed tomography (CT) and magnetic resonance (MR) imaging.

Patients with congenital **hepatic** fibrosis typically have imaging evidence of liver morphologic abnormalities, varices, splenomegaly, renal lesions, and other associated ductal plate abnormalities.

Biliary hamartomas usually manifest as multiple **cysts** that are nearly uniform in size and measure up to 15 mm in diameter.

Autosomal dominant polycystic disease typically manifests as an enlarged and diffusely cystic liver.

In Caroli disease, cystic or fusiform dilatation of the intra**hepatic** ducts is seen, as well as the "central dot sign," which corresponds to a portal vein branch protruding into the lumen of a dilated bile duct.

Choledochal cyst manifests as a fusiform or cystic dilatation of the extra**hepatic** bile duct.

Awareness of these CT and MR imaging features is essential in detecting and differentiating between various fibropolycystic liver diseases and can assist in proper management. ***(Krause et al; 2002)***.

a. Congenital Hepatic Fibrosis

Congenital **hepatic** fibrosis is a dynamic disorder that is characterized histologically by a variable degree of periportal fibrosis and irregularly shaped proliferating bile ducts ***(Benhamou J. 1999& Bernsteinet al;1988&Bayraktar et al;1997&Odievre et al;1977& Averback P. 1977).***

The term *autosomal recessive polycystic disease* is used for those cases in which renal involvement is the predominant feature. There is a progression in the extent of liver fibrosis over time, with occasional evolution into true cirrhosis of the liver ***(De Ledinghen et al; 1998).***

In most patients, the first manifestations of the disease are signs or symptoms related to portal hypertension, especially splenomegaly and varices, often with spontaneous gastrointestinal bleeding.

The timing of the onset of signs and symptoms is variable, ranging from early childhood to the 5th or 6th decade of life, although most cases are diagnosed in adolescents or young adults ***(De Vos et al; 1988).***

Liver function test results may remain normal or be only modestly elevated.

In patients with congenital **hepatic** fibrosis, there are some distinctive **hepatic** morphologic findings (along with associated abnormalities). Atrophy of the right lobe and hypertrophy of the left lateral segment and caudate lobe are common both in patients with congenital **hepatic** fibrosis and in those with advanced viral or alcoholic cirrhosis.

However, small medial segments are rarely observed in congenital **hepatic** fibrosis ***(Zeitoun et al; 2004);*** instead, the medial segment is normal in size or enlarged, a morphologic finding that may be useful in distinguishing congenital **hepatic** fibrosis from cirrhosis.

Some distinct CT features are frequently observed in association with congenital **hepatic** fibrosis, namely, liver morphologic findings (hypertrophic left lateral segment, normal or hypertrophic left medial segment, atrophic right lobe), varices, splenomegaly, associated ductal plate malformations, and renal abnormalities ***(Zeitoun et al; 2004).***

The presence of one or more associated congenital abnormalities of the biliary tree is not surprising, since all of these conditions belong to the same spectrum of ductal plate malformations.

In patients with congenital **hepatic** fibrosis, an enlarged **hepatic** artery has been described with associated large multiacinar regenerative nodules as a consequence of augmented arterialization of the liver ***(Desmet VJ. 1992).***

Because the definition of nodular regenerative hyperplasia implies that no fibrosis is interspersed between the nodules, nodules encountered in patients with congenital **hepatic** fibrosis are better defined as large regenerative nodules owing to the presence of fibrosis in the surrounding liver and the potential progression to cirrhosis.

Imaging:

a. **b.**

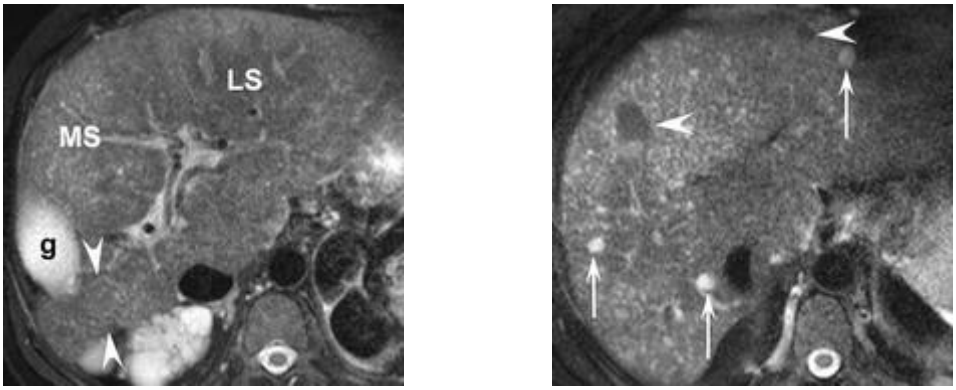


Fig. 37. **Congenital hepatic fibrosis.**

(a) Axial T2-weighted MR image shows enlargement of the lateral segment *(LS)* and medial segment *(MS)*, severe atrophy of the posterior segment (arrowheads), and renal cysts. The gall-bladder *(g)* separates the right lobe from the medial segment. Splenomegaly (not shown) was better visualized on a different section.

(b) Axial T2-weighted MR image obtained at a different level more clearly depicts the coexistence of numerous biliary hamartomas (arrows). Two hypointense regenerative nodules are also seen (arrowheads).

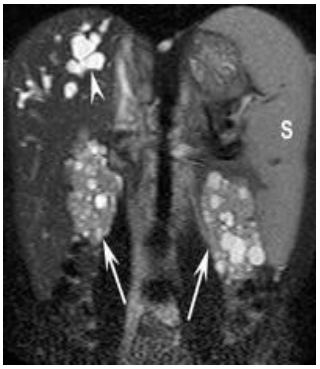


Fig. 38. **Congenital hepatic fibrosis and Caroli syndrome in a 24-year-old man. Coronal T2-weighted MR image shows splenomegaly *(S)*, multiple renal cysts (arrows), and saccular dilatation of the intrahepatic biliary tree (arrowhead), findings that are typically seen in association with Caroli disease.**

a. **b.**

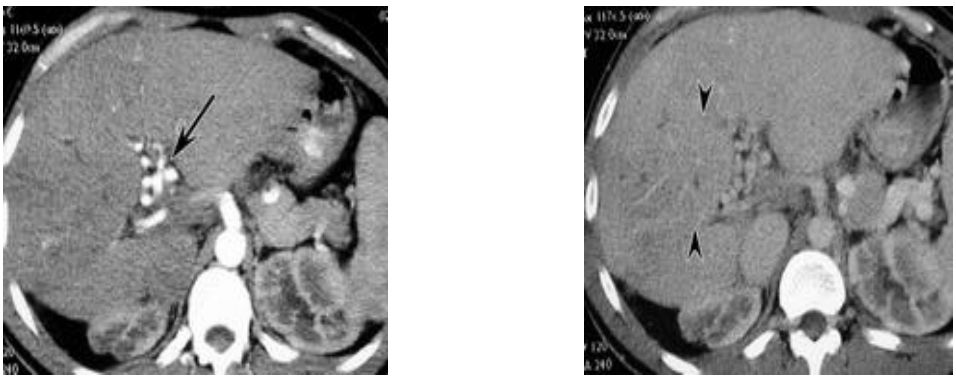


Figure 39. **Congenital hepatic fibrosis.**

(a) Transverse contrast material–enhanced arterial phase helical CT scan shows a tangled cluster of abnormally enlarged hepatic arteries at the hilum (arrow).

(b) Transverse contrast-enhanced portal venous phase helical CT scan shows a dysmorphic liver, with enlargement of the medial segment (arrowheads) and lateral segment and an atrophic right lobe. Had arterial phase images not been obtained, the hepatic arteries at the hilum could have been mistaken for portal vein cavernomatosis. In this case, there was an association of congenital hepatic fibrosis with biliary hamartomas and Caroli disease.

b. Biliary Hamartomas

Biliary hamartomas, also known as biliary microhamartomas or von Meyenburg complex, are composed of one or more dilated ductlike structures lined by biliary epithelium and accompanied by a variable amount of fibrous stroma ***(Cavallari A. 1997).***

Biliary hamartomas are typically multiple round or irregular focal lesions of nearly uniform size (up to 15 mm) scattered throughout the liver. These lesions are often discovered incidentally, and if the patient has a primary neoplasm they can be mistaken for metastatic disease.

The lesions are hypoattenuating at CT ***(Lev-Toaff et al; 1995)***, hypointense at T1-weighted MR imaging, and hyperintense at T2-weighted imaging ***(Cheung et al; 1997& Mortele et al; 2002& Slone et al; 1993& Yaziji et al; 1997).***

If the echo time is increased at T2-weighted imaging, the signal intensity of these lesions increases further and approaches that of cerebrospinal fluid. The lesions do not usually show contrast enhancement, although a peripheral enhancing rim has been described ***(Semelka et al; 1999).***

The differential diagnoses for biliary hamartomas include metastatic disease and simple **hepatic cysts** ***(Mortele et al; 2001).*** Biliary hamartomas are relatively uniform in size, whereas metastatic lesions are usually more heterogeneous in size and in attenuation or signal intensity.

Compared with biliary hamartomas, **hepatic cysts** are rarely as uniformly small or numerous, whereas the **cysts** in autosomal dominant polycystic disease are usually larger and more numerous.

The differential diagnoses for biliary hamartomas include metastatic disease and simple **hepatic cysts** (***Mortele et al; 2001***). Biliary hamartomas are relatively uniform in size, whereas metastatic lesions are usually more heterogeneous in size and in attenuation or signal intensity.

Compared with biliary hamartomas, **hepatic cysts** are rarely as uniformly small or numerous, whereas the **cysts** in autosomal dominant polycystic disease are usually larger and more numerous.

Imaging:

a.

b.

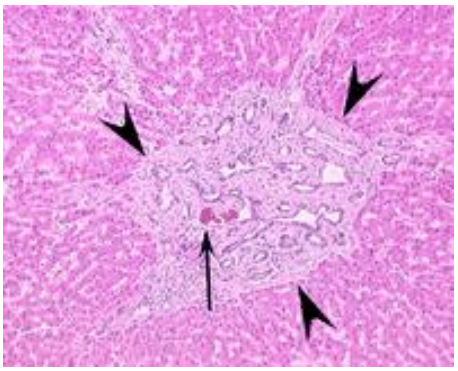
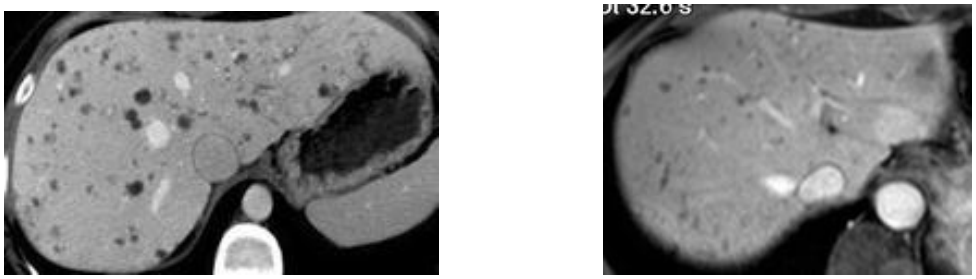


Figure 40. **Biliary microhamartomas.**
(a) Photograph of a hepatectomy specimen shows multiple 5-mm cystic lesions in the hepatic parenchyma (arrows).
(b) Photomicrograph (original magnification, x50; hematoxylin-eosin stain) shows a lesion (arrowheads) containing several cystic spaces, which are interspersed with fibrous stroma and lined by a layer of biliary epithelium. Normal hepatic parenchyma surrounds the hamartoma. Note the inspissated bile plugs within the dilated bile ducts (arrow).

a. **b.**



d. **c.**

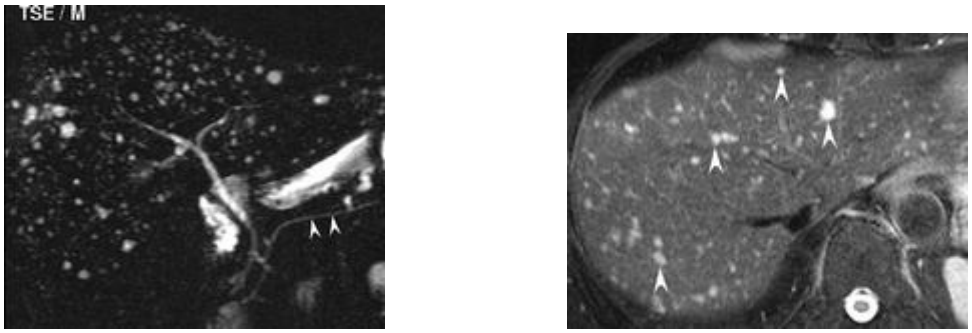


Figure 41. **Biliary microhamartomas.**

(a) Axial portal venous phase CT scan shows multiple hypoattenuating cystic lesions in both lobes that measure up to 10 mm in diameter.

(b) Axial portal venous phase T1-weighted MR image shows multiple nonenhancing hypointense lesions measuring up to 10 mm scattered throughout the liver.

(c) Axial T2-weighted MR image shows innumerable high-signal-intensity liver lesions (arrowheads).

(d) Coronal MR cholangiogram shows no communication between the cystic lesions and the normal-sized intra- and extrahepatic biliary system. Note also the normal-sized main pancreatic duct (arrowheads).

c. Caroli Disease and Caroli Syndrome

Caroli disease is characterized by multifocal segmental dilatation of the large intra**hepatic** bile ducts, which retain their communication with the biliary tree ***(Guy et al; 2002& Levy et al; 2002& Miller et al; 1995& Fulcher et al; 2001).*** The inheritance is autosomal recessive.

Two types of Caroli disease are described in the literature: Caroli disease proper, which is caused by arrested remodeling of the ductal plates of the larger intra**hepatic** ducts, and Caroli syndrome (ie, Caroli disease with congenital **hepatic** fibrosis), in which the arrest of remodeling occurs both in the early period of bile duct embryogenesis and later during the development of the more peripheral biliary ramifications ***(Desmet VJ.1992& Desmet VJ.1992).***

At radiology, Caroli disease typically manifests as saccular or fusiform cystic dilatations of the intra**hepatic** bile ducts up to 5 cm in diameter, often containing calculi or sludge.

Contrast-enhanced CT or gadolinium-enhanced MR imaging of the liver often shows fibrovascular bundles with strong contrast enhancement within dilated cystic intra**hepatic** ducts. This finding (central dot sign) ***(Choi et al;1990)*** corresponds to a portal vein branch protruding into the lumen of a dilated bile duct or a linear hyperattenuating or high-signal-intensity focus containing a portal vein and bridging the cyst wall.

Direct imaging of the biliary tree with cholangiography shows that the cystic dilatations communicate with the biliary tree. Cholangiography will show saccular or fusiform dilatations of portions of the intra**hepatic** ducts, sometimes containing filling defects representing intra**hepatic** calculi. MR cholangiography is capable of noninvasively demonstrating the communication between the cystic dilatations and the biliary tree, thus helping rule out conditions such as polycystic liver disease and biliary hamartomas.

Complications in Caroli disease are mostly due to bile stagnation, which leads to cholangitis, stone formation (predominantly bilirubin) ,and liver abscesses. If stones migrate into the common bile duct, jaundice may occur.

In Caroli syndrome, cystic biliary dilatation along with congenital **hepatic** fibrosis, portal hypertension, and hematemesis due to ruptured esophageal varices are more likely to be seen at presentation than are cholangitis or jaundice. Secondary biliary cirrhosis can occur due to biliary obstruction.

Malignancy has been described as a complication. Cholangiocarcinomas have also been reported, with a prevalence of 7% ***(Bloustein PA.1977).***

Orthotopic liver transplantation is considered in patients with diffuse liver disease that is causing frequent cholangitis or secondary biliary cirrhosis.

The differential diagnoses for Caroli disease include primary sclerosing cholangitis and recurrent pyogenic cholangitis. However, primary sclerosing cholangitis is characterized by concomitant multiple irregular strictures of the intra- and extra**hepatic** bile ducts, pseudotumoral enlargement of the caudate lobe, and a lobulated liver contour ***(Dodd et al; 1999).***

In recurrent pyogenic cholangitis, the dilatation involves the intra- and extra**hepatic** ducts and is not saccular in nature. The intra**hepatic** ducts usually show central dilatation with sudden tapering toward the periphery and are dilated both proximal and distal to the stones ***(Lim JH.1991& Federle et al; 1982).***

Imaging:

a. **b.** **c.**

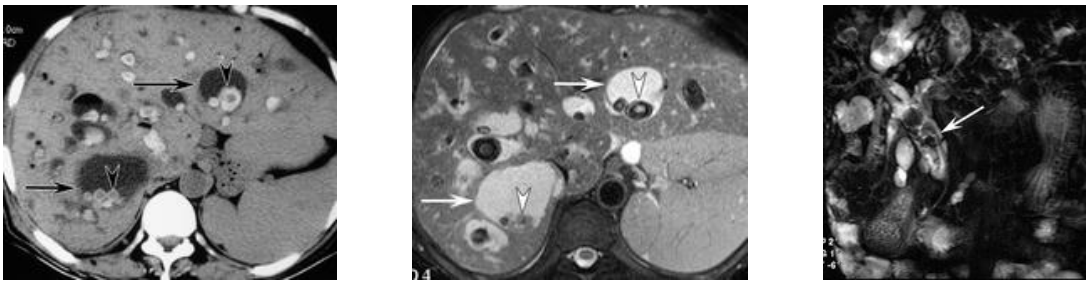


Figure 42. **Caroli disease. (a) Unenhanced CT scan shows multiple stones (arrowheads) within dilated bile ducts (arrows). (b) Axial T2-weighted MR image shows multiple hyperintense cystic ectasias (arrows) and calculi (arrowheads). (c) Coronal MR cholangiogram shows multiple dilated bile ducts with calculi. Multiple stones are seen within the dilated common bile duct (arrow). The cystic dilatations communicate with the major biliary tree.**

a. **b.**

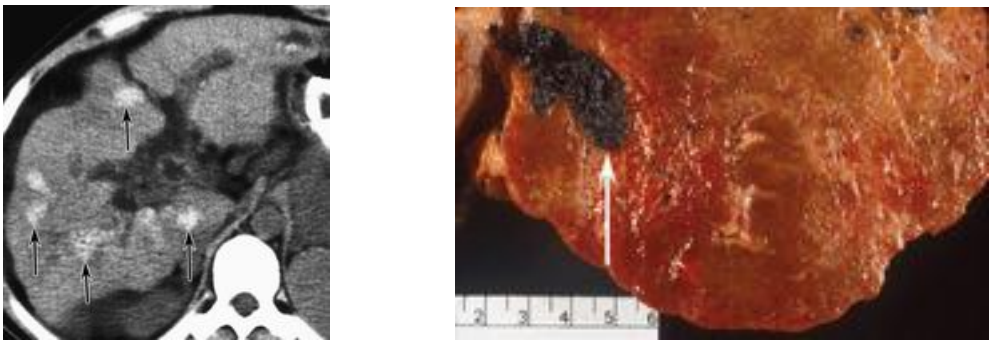


Figure 43. **Caroli disease. (a) Unenhanced CT scan shows a dysmorphic liver. Multiple stones (arrows) are seen within the bile ducts. (b) Photograph of the cut surface of the explanted liver shows multiple black bilirubin casts within the intrahepatic bile ducts (arrow). Scale is in centimeters.**

a. **b.**

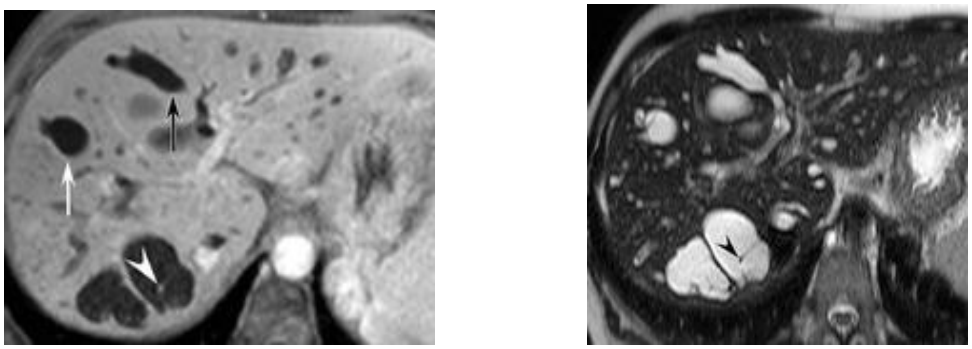


Figure 44. **Caroli disease. Axial portal venous phase T1-weighted (a) and T2-weighted (b) MR images show multiple cystic dilatations of the intrahepatic bile ducts (arrows in a). The central fibrovascular bundle (central dot sign) is also seen (arrowhead).**

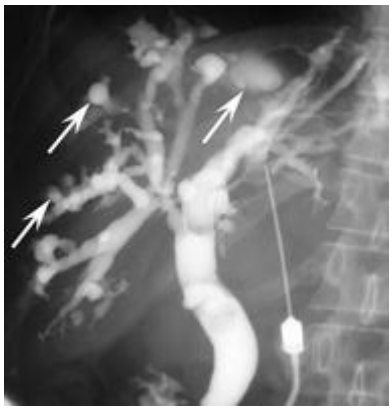


Figure 45. **Caroli disease. Percutaneous transhepatic cholangiogram shows multiple saccular dilatations of the intrahepatic bile ducts (arrows), mostly at the periphery of the liver, and fusiform dilatation of the common bile duct.**

a. **b.**

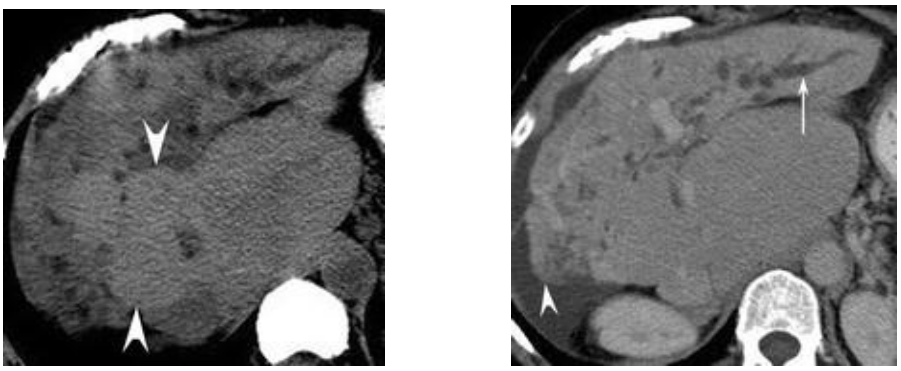


Figure 46. **Primary sclerosing cholangitis.**

(a) Unenhanced CT scan shows hypertrophy of the caudate lobe (arrowheads) and decreased attenuation of the surrounding right lobe. The relative hyperattenuation of the caudate lobe gives the appearance of pseudotumor.

(b) Contrast-enhanced CT scan better shows dilatation of the intrahepatic biliary tree (arrow). The posterior segment of the right hepatic lobe is severely atrophic (arrowhead). The elongated appearance of intrahepatic biliary dilatation in primary sclerosing cholangitis allows differentiation from the typical cystlike dilatation observed in Caroli disease.

d. Choledochal Cysts

The etiology of choledochal **cysts** remains controversial. One theory is that choledochal **cysts** are part of congenital fibrocystic disease, a ductal plate malformation of the extra**hepatic** bile duct. This theory is supported by the frequent combination of choledochal **cysts** with other intra- and extra**hepatic** disorders ***(Summerfield et al; 1986),*** with or without concomitant liver fibrosis.

Another theory is based on the presence of a pancreaticobiliary junction anomaly that predisposes to the reflux of pancreatic enzymes into the common bile duct ***(Kim et al; 2002& Kim et al; 1995& Iwai et al; 1992&Babbitt et al; 1973).*** This reflux produces chemical and inflammatory changes, with resulting weakness and dilatation of the bile duct wall.

The combination of intra**hepatic** and extra**hepatic** bile duct dilatation is designated as a type IVa choledochal cyst according to the Todani classification system ***(Todani et al; 1984).***

At imaging, choledochal **cysts** appear as cystic or fusiform dilatation of the common bile duct ***(Savader et al; 1991).***

Cholangiography best demonstrates the biliary tree and the pancreaticobiliary junction. MR cholangiography allows noninvasive evaluation of the bile duct and associated abnormalities.

Choledochal **cysts** vary greatly in size, with some of the larger **cysts** containing 5–10 L of bile. Treatment consists of complete resection of the cyst and **hepatic**ojejunostomy.

Imaging:

a. **b.**

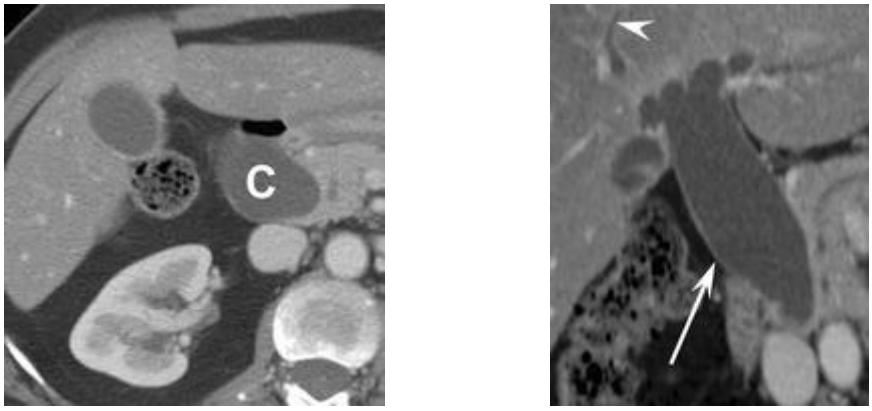


Figure 47. **Choledochal cyst (type 1).**

(a) Contrast-enhanced CT scan shows a cystic mass *(C)* well demarcated due to dilatation of the distal portion of the common bile duct.

(b) Coronal oblique multiplanar reformatted image shows fusiform dilatation of the common bile duct (arrow). Note also the dilatation of the intrahepatic biliary tree (arrowhead).

a. **b.**

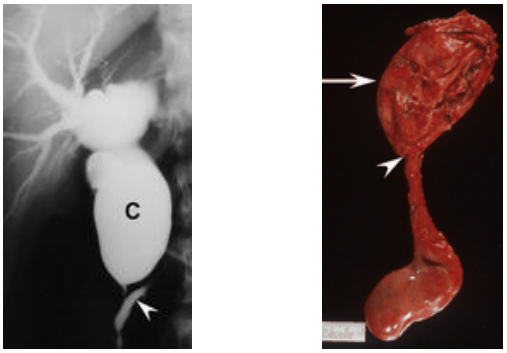


***Figure 48*.**

a. Choledochal cyst (type 1). Percutaneous transhepatic cholangiogram shows a large choledochal cyst *(C)* at the level of the extrahepatic bile duct. Note the aberrant entry of the common bile duct at the side of the pancreatic duct (arrowhead).

b. **Photograph shows an excised type 1 choledochal cyst of the common bile duct (arrow) in continuity with the cystic duct and the gallbladder (arrowhead). Scale is in centimeters.**

5.Neoplastic cysts:

Benign: Hepatic Cystadenomas.

Hepatic (biliary) cystadenomas are rare multilocular cystic tumors of the liver that are derived from the biliary epithelium and are predominantly located in the right hepatic lobe. These tumors usually involve the hepatic parenchyma (approximately *85%* of cases) and occasionally the extrahepatic biliary tract ***(Franko et al;2006).***

The size of the tumor is variable and ranges from *1.5-15 cm* in diameter; it weighs as much as *6000* grams.

In ***1892, Keen*** reported the first case of hepatic cystadenoma, which now accounts for 5% of all cystic lesions of the liver.

Hepatic cystadenomas are benign tumors, but they have a high rate of recurrence and a potential for neoplastic transformation in approximately *10%* of cases. Removing these tumors and making a proper diagnosis is important, rather than monitoring them as is appropriate for other common benign hepatic tumors, such as focal nodular hyperplasia (FNH), adenoma, and hemangioma ***(Teoh et al; 2006).***

Pathophysiology:

Hepatic cystadenomas appear as multilocular cystic lesions (rarely unilocular) that are surrounded by a smooth and thick fibrous capsule. The tumors contain numerous internal septations and intraluminal papillary projections, which are lined by mucous-secreting cuboidal or columnar biliary epithelium ***(Terada et al; 1997).*** This epithelium is sometimes surrounded by a dense mesenchymal stroma containing smooth-muscle cells. A loose layer of collagen-containing blood vessels, nerves, and bile ducts further surrounds this area. True connections with the biliary tree are rare.

Traditionally, cystadenomas are thought to originate from the biliary epithelium, possibly from a congenitally aberrant bile duct. Other possibilities are that the tumors arise directly from embryonic foregut cells or peribiliary endocrine cells.

Two types of hepatic cystadenomas are described pathologically, as follows: ***mucinous*** and ***serous***. *Mucinous cystadenoma* is the predominant type (95% of cases) that occurs in women. They are located in the intrahepatic region (84%), the common bile duct (6%), the hepatic ducts (4%), and the gallbladder (2%).

Frequency:

The prevalence of hepatic cystadenomas is low. These tumors account for a very small number of all hepatic tumors.

Mortality/Morbidity:

Because of their premalignant potential, untreated lesions carry significant mortality. Some authors report a malignant transformation rate of as high as 20-30% ***(Woods GL; 1981).*** However, in most series, hepatic cystadenomas carry an extremely low risk of mortality and morbidity after proper surgical resection.

Race:

The true prevalence of cystadenomas in different races is unknown.

Sex:

Most tumors (80-85%) occur in women. The etiology of cystadenoma is unclear, but hormonal involvement is possible.

Age:

The peak frequency of hepatic cystadenomas is in patients aged 30-50 years (mean age, 41.7-53.4 y), with two thirds of cases occurring in patients aged 40 years or older. These tumors may arise as early as the first or second decade of life; however, they are extremely rare in children.

Clinical Findings:

History:

Hepatic cystadenomas are often discovered incidentally at a routine physical examination or on imaging studies, such as ultrasound (US) or CT scan. Less frequently, nonspecific symptoms related to compression of a neighboring organ may be noted. Presenting symptoms depend on the size and the location of the lesion. The final diagnosis is made after surgical resection. ***Roughly 15% of patients present with***:

a. Small intrahepatic lesions, which are usually asymptomatic and discovered incidentally after screening ultrasonography.
b. For larger lesions, the typical presentation is that of an expanding mass in the right upper quadrant accompanied by pain, nausea, vomiting, and, in selected cases, cholangitis and sepsis.
c. Unusual presentations include obstructive jaundice, ascites secondary to portal vein compression, and intracystic hemorrhage.
d. Acute abdomen is a rare presentation and may be caused by the rupture of the cystic wall, intra-peritoneal hemorrhage, or cyst torsion ***(Catinis et al; 1988).***

Physical examination:

Physical examination findings from patients with hepatic cystadenomas are usually unremarkable unless the tumor has reached a significant size and causes compressive symptoms.

Physical examination may reveal:

a. A palpable and tender mass in the right upper quadrant or epigastrium.
b. Hepatomegaly (less common).
c. Lower-extremity edema and/or signs of portal hypertension may occur in patients with lesions large enough to compress the portal vein or vena cava.

d. Splenomegaly may be an indication of a compressive effect on the portal circulation, with development of portal hypertension. These patients also may develop ascites.
e. Jaundice suggests obstruction of the biliary system. Rare extension of the lesion in a pedunculated fashion inside the biliary system ***(Dardik et al; 1964).***
f. Obstruction of the inferior vena cava may cause marked lower-extremity edema.
g. In the rare occurrence of intraperitoneal rupture of the lesion, the patient may have signs typical of acute peritonitis.

Causes:

- The etiology of hepatic cystadenomas is unknown.
- The resemblance of embryonic structures, such as the gallbladder and the biliary tree, originating from the foregut suggests that these lesions arise from ectopic remnants. The fact that these tumors have been described as early as the first decade of life supports this theory.
- Immunohistochemistry and electron microscopy studies have contradicted the possible origin of these tumors from ectopic ovarian tissue.
- Environmental factors may play a significant role. Most tumors appear later in life.
- The marked female preponderance suggests a role for hormonal influence.

Differential Diagnoses:

- Hepatic Cysts.
- Hepatocellular Adenoma.

Other Problems to Be Considered:

- Hepatic cystadenomas are considered in the differential diagnosis of other hepatic cystic lesions, including simple cysts, echinococcal cysts, and cystadenocarcinomas.
- Intracystic hemorrhage, septations, or mural nodularity can be present both in cystadenomas and in other cystic lesions.
- Less commonly, cystadenomas may be confused with necrotic neoplasms, cystic metastases, abscesses, cystic hamartomas, embryonal sarcomas, hematomas, or other congenital cysts.
- Diagnostic questions also may arise in patients with Caroli disease or other forms of polycystic liver disease.
- Multiple bile duct hamartomas (*von Meyenburg complex*) can also mimic biliary cystadenoma, both for presentation and for imaging ***(Karahan et al; 2007).***

Laboratory Studies:

Although liver test results may be normal in patients with biliary cystadenomas, elevation of alkaline phosphatase, bilirubin, and, less commonly, aminotransferase levels can be present.

Superinfection of the tumor may cause leukocytosis with a left shift. Anemia is extremely rare but theoretically possible secondary to bleeding.

Carbohydrate antigen (CA) 19-9 levels may be elevated in some cases. Carcinoembryonic antigen (CEA) and alpha-fetoprotein levels are usually normal ***(Horsmans et al; 1996).***

Cyst fluid analysis at laparoscopy has been proposed in the surgical management of hepatic cysts. Elevated intracystic CA19-9 values were found in biliary cystadenomas compared to those of simple cysts ***(Koffron et al; 2004).***

Imaging Studies:

Imaging studies are the key element of the workup.

On **US**, hepatic cystadenomas appear as anechoic lesions with internal septations. Focal hyperechoic areas within the lesion are common and can represent focal wall fibrosis, intracystic hemorrhage, or papillary projections.

On **CT** scan, the tumor appears as low-attenuation water density areas with focal enhancement after contrast administration. The septa and the mural nodules often are visualized. Involvement or compression of the portal vein and biliary tree can be appreciated best by CT scan ***(Kanamori et al; 1985).***

MRI can help provide additional information about the nature of the cystic fluid (ie, hemorrhagic vs serous or mucinous). Lesions appear hyperintense on T2-weighted images and hypointense on T1-weighted images, sometimes with reduced perilesional rim signal intensity on T2-weighted images.

Intracystic hemorrhage produces higher signal intensity on T1-weighted images than mucinous or bilious fluid content ***(Baudin et al; 2006).***

US is more sensitive in identifying internal septations, whereas CT scan provides anatomical relation to the liver.

Other Tests:

Endoscopic retrograde cholangiopancreatography (ERCP) may demonstrate intraluminal filling defects or a cystic cavity communicating with the biliary tree. Apart from helping in the diagnosis of a cystadenocarcinoma, ERCP is also helpful in decompressing the biliary system in patients with biliary obstruction.

Magnetic resonance cholangiopancreatography (MRCP) is an alternative to ERCP in the evaluation of pancreatic and biliary duct

systems. Even though the resolution of MRCP is somewhat inferior to ERCP, the procedure is noninvasive and less expensive.

Procedures:

**Fine-needle aspiration biopsy*:

- Initial imaging studies should be followed by fine-needle aspiration (FNA) biopsy of the liver, which may help provide important information about the nature of the lesion.
- *Cytology of the fluid* or FNA of prominent papillary projections or wall nodules is useful in helping clarify the diagnosis, even though dissemination of malignant cells through the needle track is a theoretical concern.
- The authors usually choose to proceed with FNA biopsy whenever a question exists regarding the diagnosis of a hepatic tumor.
- However, remember that needle biopsy findings from hepatic cystadenomas may be misleading because foci of adenocarcinomas can be easily missed.
- If the diagnostic suspicion of a hepatic cystadenoma is high, a direct referral for surgical resection is indicated.

*A laparoscopic approach with cyst fluid analysis for CA19-9 and CEA followed by cyst wall tissue sampling has been proposed. Elevated CA19-9 levels and premalignant or malignant histology should be followed by radical resection ***(Koffron et al; 2004).*** .

Histologic Findings:

Solid hepatic lesions may be considered in the differential diagnosis, especially when the lesions appear irregular on imaging studies. Such lesions include FNH, adenomas, angiomyolipomas, and primary hepatic malignancies, such as hepatocellular carcinoma and cholangiocarcinoma.

A histological variant of biliary cystadenoma occurring primarily in women has been described as cystadenoma with mesenchymal stroma. This variant is characterized by the presence of spindle cells in the mesenchymal stroma that are capable of differentiating into different cell types, with a high premalignant potential ***(Wheeler et al; 1985).***

Differentiation of cystadenomas from cystadenocarcinomas is particularly difficult. Imaging studies are not sensitive enough to completely exclude the presence of malignant degeneration in a cystadenoma.

Determination of the tumor marker CA19-9 in the serum and in the cyst fluid has been suggested, but CA19-9 also can be expressed in the biliary epithelium lining of benign cystadenomas.

For this reason, the presence of CA19-9 is not 100% reliable in the diagnosis of cystadenocarcinoma ***(Ishak et al; 1977).***

Embryonal sarcoma also is in the differential.

Cystadenomas may express a progesterone receptor in the mesenchymal cell component. Other markers demonstrated on immunohistochemistry are CA19-9, CEA, vimentin, and cytokeratin ***(Grayson et al; 1966).***

In situ hybridization has demonstrated selective positivity for albumin messenger RNA in cystadenocarcinomas ***(D'Errico et al; 1998).***

Available evidence shows that biliary cystadenomas tend to occur predominantly in women because these tumors are hormonally responsive. This theory is further supported by immunohistochemical studies demonstrating positive estrogen/progesterone receptors associated with biliary cystadenomas ***(Abdul-Al HM et al; 2007).***

Treatment:

I) Medical Care:

No medical treatment has been found to be effective. Discontinuing hormonal treatment until the estrogen/progesterone receptor studies are completed is prudent.

II) Surgical Care:

- The treatment of choice for hepatic cystadenomas is surgical resection. Complete resection of the tumor is imperative to avoid local recurrence and malignant transformation ***(Jenkins et al; 1994&Sanchez et al; 1991).***
    - A complete lobectomy is sometimes necessary for larger lesions or in the presence of adenocarcinoma ***(Ramacciato et al; 2006).***
    - For smaller lesions, enucleation alone can usually be accomplished with preservation of the remaining hepatic parenchyma unless the tumor is in a central location close to the hepatic hilum. Enucleation is possible because cystadenomas have a thick fibrous capsule that can be dissected bluntly without major bleeding or biliary leak ***(Shimada et al; 1998).***
- Surgical mortality is not higher than mortality associated with a corresponding hepatic resection or lobectomy.
- Liver transplantation may be necessary in the rare occurrence of extensive bilobar extension of the tumor.

Diet:

No specific diet is recommended. In the presence of biliary obstruction, deficiency of fat-soluble vitamins should be corrected.

Activity:

Activity is usually not restricted. However, after surgical intervention, standard precautions as in other abdominal surgery should be taken.

Follow-up:

Further Outpatient Care:

No further outpatient care is indicated routinely after complete surgical resection. However, because local recurrence of a cystadenoma with progression to cellular atypia and, ultimately, carcinoma has been described, regular postoperative follow-up is indicated.

Follow-up is conducted best by performing abdominal US or CT scan at 6-month intervals for the first postoperative year and then annually.

Complications:

- Bleeding
- Rupture
- Obstructive jaundice
- Malignant transformation
- Infection
- Gastric outlet obstruction
- Ascites
- Inferior vena cava obstruction

Prognosis:

The prognosis of hepatic cystadenomas is extremely good if patients undergo a complete surgical resection. Improper treatment, such as marsupialization, internal Roux-en-Y drainage, or percutaneous drainage and alcoholization, is associated with almost certain recurrence. In particular, aspiration or partial excision of cystadenomas is associated with a recurrence rate of higher than 90%.

Summary

Benign hepatic tumors include a broad spectrum of regenerative and true neoplastic processes.

Because of advances in imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI) as well as progress in immunohistochemistry, accurate diagnosis can now be made in a large percentage of patients without surgical laparotomy or resection.

Many of these tumors present with typical features in various imaging studies. On occasions, biopsies are required and/or surgical removal is needed.

The most common benign hepatic tumors include cavernous hemangioma, focal nodular hyperplasia, hepatic adenoma, and nodular regenerative hyperplasia.

In the majority of cases of benign hepatic tumors, patients are asymptomatic, and no treatment is indicated. The main indication for treatment is the presence of significant clinical symptoms or suspicion of malignancy or fear of malignant transformation.

Benign hepatic tumors can be categorized as solitary or multiple and as solid or cystic. In general, a single imaging study is insufficient for a definitive diagnosis, and further studies may be necessary.

Most benign hepatic tumors follow a fairly indolent clinical course. However, some of them are associated with serious complications. Thus, the understanding of clinical, radiologic, and pathologic characteristics of each tumor is important for accurate diagnosis and appropriate treatment of these tumors.

Hemangiomas

Hemangiomas are the most common benign liver neoplasms, and are seen more commonly in young adult females. They are frequently multiple, in around 70% of patients.

Pathologically they are comprised of vascular lakes and channels, some of which can develop thrombosis and fibrosis.

Variants include giant hemangiomas that can occupy up to the entire hepatic lobe, and may expand the liver contour. On rare occasions hemangiomas can hemorrhage, and another rare feature is transient early perilesional enhancement.

Focal Nodular Hyperplasia

The etiology of these lesions is unclear, but the histopathological findings may be related to an underlying developmental abnormality, with a hyperplastic response of liver parenchyma and a disorganized growth pattern of hepatocytes and ducts.

The lesion forms as an unencapsulated mass, with central stellate fibrovascular core with malformed vessels and bile duct proliferation. They are more common in young adult females, most likely related to hormonal stimulation, and regress with age. They can be multiple. They apparently have no malignant potential, and hemorrhage is exceedingly rare.

Treatment includes conservative clinical follow-up in asymptomatic patients. Surgical resection is indicated for those with significant symptoms or in whom malignancy cannot be excluded by radiologic and histologic studies.

Hepatic Adenoma

Hepatic adenoma is a benign epithelial neoplasm. The majority of lesions occur in young females, <40 years of age, on oral contraceptives. Lesions will involute to a variable extent if oral contraceptives are discontinued.

The patient can present with abdominal pain related to spontaneous intralesional hemorrhage, and can rarely bleed extensively into the peritoneum and require emergency intervention.

Histopathology shows 2–3 layer sheets of normal hepatocytes separated by sinusoids and thin veins with areas of microhemorrhage. There are no bile ducts and a pseudocapsule may form due to compressed adjacent liver.

Liver adenomatosis represents a rare and distinct entity, with equal incidence in males and females. Steroid association may be absent. This entity is associated with abnormal elevated liver enzymes, and has a higher risk of hemorrhage and of malignant transformation. Generally multiple lesions (>10) are present, which exhibit irregular enhancement.

Granulomas

Various mycobacterial organisms can involve the liver. Tuberculosis is globally the most common cause of infectious hepatic granulomas. There is an increased incidence in patients with AIDS.

Mycobacterium avium intracellulare (MAI) is the most common hepatic infection in AIDS, found in 50% of autopsy specimens.

Various fungal organisms might involve the liver. Patients are typically immunocompromised. *Candida albicans* is the most common

type of fungal disease, and often additionally involves the spleen, and occasionally the kidneys.

Macroregenerative Nodule

MRN is a benign but premalignant lesion found in cirrhotic or fibrotic livers. Imaging findings are not characteristic, but MRI findings are useful for the differentiation from HCC.

Because of its malignant potential, surgical resection of MRN is sometimes advocated, especially in those with atypia.

Optimal management of MRN remains unknown pending ongoing investigation.

Benign Bile Duct Hamartoma

Biliary hamartomas are benign and relatively common, occurring in 3% of the population. Pathologically they are comprised of small irregular branching bile ducts that may be dilated and embedded in a fibrous stroma.

Hepatic Cysts

Cysts are commonly found in adults. The etiology is unclear, but may result from different mechanisms, including developmental and acquired causes. Underlying pathology generally shows single layer lining with cuboidal to columnar epithelial cells.

Complications such as intracystic hemorrhage or infection are very rare. Management includes conservative observation, laparoscopic or open surgical treatment.

Cystic lesions of the liver include simple cysts, multiple cysts arising in the setting of polycystic liver disease (PCLD), parasitic or hydatid (echinococcal) cysts, cystic tumors, and abscesses. These

conditions can usually be distinguished on the basis of the patient's symptoms and the radiographic appearance of the lesion. Ductal cysts, choledochal cysts, andV Caroli disease are differentiated from hepatic cysts by involvement of the bile ducts.

Echinococcal Cyst

Hydatid cysts are caused by tapeworm infection, which has a worldwide distribution. Most patients are asymptomatic.

Diagnosis is made by eosinophilia, positive serologic tests, and characteristic imaging features. Treatments include medical, surgical, and laparoscopic procedures.

Echinococcal abscesses arise from two types of organisms, *E. granulosis* and *E. alveolaris*. *E. granulosis* causes hydatid cyst and is found in North America, Europe, and Asia, with sheep as a primary host, and humans are accidental carriers.

Cysts are spherical and form a fibrous rim. Typically, there is little tissue reaction, unless the cyst ruptures and leaks fluid that can induce a marked inflammatory reaction.

Infectious and Inflammatory cysts

A variety of infectious agents may involve the liver, some of which have a distinctive appearance. Below is a description of some of the most important of these.

Pyogenic abscess shows central purulent necrosis with a relatively hypo- or avascular core quickly forming a surrounding rind of vascularized granulation tissue. Increasing fibrous tissue occurs with time. The most common cause is bacteria entering the portal venous system seeding liver from a bowel source, related to diverticulitis, appendicitis, or Crohn's disease.

Non-pyogenic abscesses include amoebic, echinococcal, myocobacterial, and fungal. Amebic abscesses are generally due to entamoeba histolytica, and these lesions are rare in industrialized countries and usually related to travel in the tropics.

Clinically, patients present with a septic picture, including nausea, vomiting, and weight loss. Histologically, necrosis secondary to obstruction of venules by the trophosites and by-products is present.

Choledochal cyst

Choledochal cyst is a congenital bile duct anomaly. US findings are diagnostic in many patients; however, complementary studies such as CT, MRI/MRCP, or PTC/ERCP may be helpful in the preoperative period for delineating details of the surrounding anatomy. The best treatment is complete excision with biliary-enteric reconstruction.

Hepatic cystadenomas

Hepatic (biliary) cystadenomas are rare multilocular cystic tumors of the liver that are derived from the biliary epithelium and are predominantly located in the right hepatic lobe. These tumors usually involve the hepatic parenchyma (approximately 85% of cases) and occasionally the extrahepatic biliary tract. The size of the tumor is variable and ranges from 1.5-15 cm in diameter; it weighs as much as 6000 grams.

Hepatic cystadenomas are benign tumors, but they have a high rate of recurrence and a potential for neoplastic transformation in approximately 10% of cases.

CONCLUSION

1. The key to managing patients with benign liver tumors is an accurate diagnosis and knowledge of the natural history of the untreated lesion.

   - Does the patient have symptoms or was the lesion detected incidentally?
   - Do other clinical characteristics such as the patient's age, gender, use of oral contraceptives, history or risk factors for chronic liver disease or cirrhosis, and history or findings of extrahepatic malignancy provide clues?
   - Is there a travel history or are there other features suggesting an amebic or pyogenic abscess?

All of these considerations must then be integrated with the findings of appropriate imaging studies. Histological confirmation should be obtained to reach an accurate diagnosis when necessary. The combination of the above features will reveal the correct diagnosis in the majority of patients.

2. Increasing experience, improved techniques, and better support systems have made hepatic surgery a safe and effective therapeutic modality.
3. However, as we have learned more about the prognoses of certain lesions (particularly hemangioma and FNH), a more conservative attitude has evolved, particularly since improvements in noninvasive imaging now permit careful follow-up by serial examinations.

4. Some benign tumors may be safely observed, others require resection, and it is ultimately the surgeon's responsibility to determine the most appropriate course of action. As discussed before, such decisions are not always simple or straightforward and often require significant experience and mature clinical judgment.
5. An otherwise fit patient with a symptomatic benign hepatic tumor should be considered for resection, provided that the tumor can be removed safely. It is imperative to ensure that the symptoms are indeed related to the tumor and do not arise from some other abdominal pathology.
6. **Fine needle biopsy**: is commonly used to assist in the diagnosis of a variety of liver lesions. However, a number of controversial issues surround the role of FNA in this setting. ***First***, it is commonly nondiagnostic when used to evaluate some types of liver lesions such as hepatic adenomas and focal nodular hyperplasia. ***Second***, it is associated with some degree of risk, including bleeding and seeding of neoplastic cells.

Recommendations

1- Clinical parameters, imaging studies and laboratory tests are recommended to be used as follow up method to replace liver biopsy and avoid its major complications.

2- A need to develop a scoring system based on clinical and laboratory parameters for proper evaluation of the liver pathology similar to histopathological grading and staging system.

3- Protocol of management of focal hepatic lesions susceptible patients; e.g. Diabetics, Oral contraceptives users and Glycogen storage disease.

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