Summary of SCH Imaging labs

Study: Ultrasound abdomen; Date: 4/9/2013 at 11:48 PM
Comparison: Abdominal radiographs 4/9/2013 at 8:26 PM.
Technique: Solid abdominal organs and retroperitoneum were evaluated in real-time sonographically.
Findings:
The liver is normal in size and echogenic texture. There is no focal hepatic mass. ….

Study: Ultrasound abdomen with Doppler evaluation: April 10, 2013 at 0915 hours.
Comparison: Abdominal ultrasound dated April 9, 2013 at 2348 hrs.
Technique: Solid abdominal organs and retroperitoneum were evaluated in real-time sonographically. Grayscale,color and spectral Doppler evaluations were performed.
Gray-scale findings:
The liver appears somewhat edematous exhibiting decreased through transmission.

Examination: CT angiogram of the abdomen; Date: 4/11/2013 at 3:53 PM
Comparison: Abdominal Doppler 4/10/2013; abdominal ultrasound 4/9/2013; chest/abdomen radiograph
4/9/2013.
Findings:
Thorax: …
Abdomen:
The liver demonstrates several subcentimeter hypodense lesions, the majority of which are located in the right lobe. The largest of these lesions is located in segment six and measures 7 x 6 mm (series 4 image 40).

Result

********** FINAL REPORT **********

Name: XIE,JIANHUA DRACO **ID #:** 1275567

Exam: US ABDOMINAL SONOGRAM At 2348 Hours **Acc#:** US1304310

Exam Date: 20130409 **Physician:** Davis Jeremiah C

***** FINAL REPORT *****

Results
Clinical History: 6-month-old with abdominal distention, body wall edema, abdominal x-ray with paucity of gas and bowel wall thickening. Please evaluate for etiology of abdominal distention and swelling.

Study: Ultrasound abdomen; Date: 4/9/2013 at 11:48 PM

Comparison: Abdominal radiographs 4/9/2013 at 8:26 PM.

Technique: Solid abdominal organs and retroperitoneum were evaluated in real-time sonographically.

Findings:
The liver is normal in size and echogenic texture. There is no focal hepatic mass. The gallbladder is normal in size. Gallbladder wall demonstrates mild diffuse thickening. There is no cholelithiasis. There is no pericholecystic fluid. The common bile duct measures 1.2 mm. There is no intrahepatic biliary dilatation.

There is mild splenomegaly, measuring 8.5 cm. (normal range 5.2-7.0 cm). Splenic echogenic texture is normal.

The pancreas is poorly visualized, but demonstrates no gross abnormality. The right kidney measures 5.6 cm in length. The left kidney measures 6.0 cm in length. Normal renal length for age is 6.2 cm +/- 1.3 cm. There is trace bilateral pelviectasis. Renal parenchyma is unremarkable. The urinary bladder is decompressed, but demonstrates no focal abnormality. There is no distal ureteral distention.

Visualized images of the abdominal aorta and IVC are unremarkable.

There is a moderate amount of intraperitoneal free fluid.

Impression:

1. Moderate intraperitoneal free fluid.
2. Mild diffuse gallbladder wall thickening without cholelithiasis or pericholecystic fluid, likely related to volume overload with third spacing of fluid.
3. Mild splenomegaly.
4. Trace bilateral pelviectasis (SFU grade 1).

Results conveyed to Dr. Jeremiah Davis by Dr. Jebb Baker at 12:10 AM on 04/10/2013.
Resident: Baker, Joe Blunt, MD

I have personally reviewed this study
and agree with the report above.

SEP/JBB Radiologist: Parnell, Shawn E, MD
APPROVED

Result

********** FINAL REPORT **********

Name: XIE,JIANHUA DRACO **ID #:** 1275567

Exam: US ABDOMINAL DOPPLER COMPLETE+US ABD CMP At 0915 Hours

Acc#: US1304312

Exam Date: 20130410

Physician: Davis Jeremiah C

***** FINAL REPORT *****

Results
Clinical History: 6 month old male with apparent liver failure

Study: Ultrasound abdomen with Doppler evaluation: April 10, 2013 at 0915 hours.

Comparison: Abdominal ultrasound dated April 9, 2013 at 2348 hrs.

Technique: Solid abdominal organs and retroperitoneum were evaluated in real-time sonographically. Gray-scale, color and spectral Doppler evaluations were performed.

Gray-scale findings:

The liver appears somewhat edematous exhibiting decreased through transmission. Best appreciated with the use of a high-resolution transducer, is the interval development of multiple small echogenic foci throughout the right lobe of the liver. These foci do not seem to be related to the portal triads. The largest and most conspicuous of these lesions is seen with linear transducer and is located in the inferior aspect of the right lobe of the liver, inferior to the main portal vein, likely in segment 6. This measures 0.8 x 0.6 cm.

The gallbladder is contracted, possibly secondary to nonfasting state. There is no pericholecystic fluid.

The common bile duct is not well visualized. There is no intrahepatic biliary dilatation.

As before, the spleen is enlarged measuring 8.4 cm, unchanged. Extreme upper limits of normal splenic size for patient age is 7 cm. No focal splenic abnormality is seen.

The pancreas is obscured secondary to bowel gas.

The kidneys are symmetric in size. The right kidney measures 5.8 cm, previously 5.6 cm. The left kidney measures 5.7 cm, previously 6 cm. Mean expected renal length for patient age is 6.2 cm with 2 standard deviations of 1.3 cm. The kidneys are normal in position, contour, and echogenicity. There is no evidence of renal mass or stone. Trace central pelviectasis on the right has decreased since prior; there is no dilatation of the left renal collecting system.

There is neither proximal nor distal ureteral dilatation. The urinary bladder is only minimally distended, precluding complete assessment but is grossly unremarkable.

There is a small amount of free intraperitoneal fluid present primarily superior and anterior to the liver. No pleural effusion.

Visualized images of the abdominal aorta and IVC at the level of the liver are unremarkable.

There is incidental note of the presence of some loops of bowel in the right upper quadrant, superior and anterior to the liver, a normal variant.

Doppler findings:

The hepatic arteries are patent with sharp upstrokes. Resistive indices are within elevated, and are as follows:

HA extrahepatic: 1.0.
PHA: 1.0. There is incidental note of a slightly reverse component to the waveform.
RHA, anterior: 1.0.
RHA, posterior: 1.0.
LHA: 1.0.

The portal veins are all patent with normal waveforms and expected hepatopetal flow. Velocities (cm/s) are as follows:

MPV, extrahepatic: Obscured by bowel gas.
MPV, intrahepatic: 36; borderline pulsatile.
RPV, anterior: 34.
RPV, posterior: 39.
LPV: 30.

The splenic artery is patent within elevated RI=0.88. The splenic vein is obscured by bowel gas precluding assessment.

The hepatic veins are all patent with expected hepatofugal flow. There is biphasic flow within the main, left and right hepatic veins.

The IVC is patent. The visualized aorta is unremarkable.

There is incidental note of patency/recanalization of the umbilical vein with velocity of 31 cm/s.

The SMV is obscured by bowel gas.

Impression:

1. Edematous appearance to the liver with interval development of multiple small echogenic foci throughout the right lobe of the liver, the latter findings suggesting a diffuse inflammatory etiology including septic emboli. Differential diagnosis for the echogenic hepatic foci includes metastatic lesions and the possibility of hemorrhagic infarcts.

2. Persistent splenomegaly.
3. Contracted gallbladder likely reflecting nonfasting state.
4. Trace central pelviectasis right kidney, decreased from prior.
5. Small amount of anechoic free intraperitoneal fluid.
6. Abnormally elevated resistive indices measuring 1.0 throughout the liver.
7. Recanalization/patency of the umbilical vein, a finding which, in conjunction with splenomegaly, suggests portal hypertension.

Critical result of new, diffuse echogenic foci throughout the right lobe of the liver (as well as the other above findings) conveyed to Dr.Yaghami, PICU fellow, at completion of imaging at approximately 1030 hrs. on April 10, 2013. Tiny was also reviewed with Dr.Shu GI attending, at approximately 1130 hrs. on 4/10/2013.
MTP/MTP Radiologist: Parisi, Marguerite Theresa, MD, MS
APPROVED

Result

********** FINAL REPORT **********

Name: XIE,JIANHUA DRACO **ID #:** 1275567

Exam: CT ANGIO ABD WITH CONTRAST At 1621 Hours **Acc#:** CT1302517

Exam Date: 20130411 **Physician:** Turnbull Jessica M

***** FINAL REPORT *****

Results
Clinical history: 6-month-old with newly diagnosed liver failure of unknown etiology. Liver ultrasound concerning for possible metastasis from unknown primary. Please evaluate for metastasis, lesions concerning for malignancy.

Examination: CT angiogram of the abdomen; Date: 4/11/2013 at 3:53 PM

Comparison: Abdominal Doppler 4/10/2013; abdominal ultrasound 4/9/2013; chest/abdomen radiograph 4/9/2013.

Technique: After the oral administration of contrast as well as uneventful intravenous injection of 19 cc of Optiray, 1.25 mm axial sections were reconstructed from helical acquisition from the diaphragm through the iliac crests during the arterial phase of contrast enhancement. Next, 2.5 mm axial sections were reconstructed from helical acquisition from the lung apices through the initial tuberosities during the portal venous phase of contrast enhancement. 2-D coronal and sagittal as well as axial and coronal MIP reformations were performed.

Findings:

Thorax:
Right arm PICC terminates at the cavoatrial junction.

There are bilateral dependent airspace opacities. There is a 4 mm in the right upper lobe (series 33 image 20).

There is no pleural fluid or thickening. There is no mediastinal or hilar adenopathy. Residual thymic tissue is noted. The heart is normal in size. There is no pericardial effusion or thickening. The chest wall demonstrates diffuse subcutaneous edema, slightly more prominent in the axillary regions bilaterally. No axillary or supraclavicular adenopathy is demonstrated.

Abdomen:
The liver demonstrates several subcentimeter hypodense lesions, the majority of which are located in the right lobe. The largest of these lesions is located in segment six and measures 7 x 6 mm (series 4 image 40). The majority of the hepatic lesions demonstrate fat attenuation. There is mild periportal edema.

There is moderate splenomegaly, measuring up to 86 mm in maximum dimension (series 607 image 32).

There is diffuse haziness throughout the mesentery. The mesenteric vessels appear somewhat stretched, but do not appear to be compressed. There is similar haziness throughout the retroperitoneal fat. There is no focal mass demonstrated. There is also likely a small amount of intraperitoneal free fluid. There is enteric contrast throughout the bowel to the level of the hepatic flexure. There is a transient small bowel-small bowel intussusception in the left lower quadrant (series 4 image 83). There is diffuse wall thickening and mucosal hyperenhancement involving the sigmoid colon and rectum. There is no evidence of bowel obstruction. The

appendix appears to be normal in caliber, but is somewhat difficult to evaluate given the degree of diffuse mesenteric fat stranding/infiltration.

There is recanalization of the paraumbilical vein, but this remains small in caliber. There are minimal gastric varices noted, most apparent on coronal images (series 607 image 37). The splenic, superior mesenteric and main portal veins are patent. The celiac, superior enteric, inferior mesenteric and renal arteries are patent and demonstrate normal branching patterns. There is no anomalous vessel demonstrated.

There is a moderate sized fluid filled umbilical hernia. There is diffuse body wall edema.

There is no definite mesenteric lymphadenopathy. No apparent retroperitoneal adenopathy.

The gallbladder is normal in caliber with no radiopaque stone demonstrated. The common bile duct is normal in caliber. There is no intrahepatic ductal dilatation. The adrenal glands demonstrate no significant abnormality. The kidneys are normal in size without hydronephrosis, stone or mass. The pancreas is normal in size without focal mass.

Pelvis:
Urinary bladder is fluid-filled and demonstrates no focal abnormality. There is no mass or focal fluid collection. There is no apparent lymphadenopathy.
Therefore
Bones:
No acute osseous abnormality. No lytic or sclerotic osseous lesion.

Impression:

1. Diffuse hazy mesentery could represent edema in the setting of stigmata of portal hypertension including recanalized paraumbilical vein, minimal gastric varices and moderate splenomegaly as well as diffuse subcutaneous edema. Additional diagnostic considerations include infectious processes of the mesentery given coexisting bowel wall thickening and mucosal hyperenhancement of the sigmoid colon or possibly an infiltrative process of the mesentery such as lymphoma or leukemia.

2. Numerous small hypodense hepatic lesions are too small to further characterize and are thus indeterminate. However, diagnostic considerations should include infection or metastases. Fat density is seen within several lesions and therefore fat containing metastases such as liposarcoma can produce this pattern although there is no evidence of primary tumor on the current exam, benign fat-containing lesions such as angiomyolipomas, xanthomas could be included in the differential of fat containing lesions.

3. Sigmoid colon and rectal wall thickening with mucosal hyperenhancement could represent infectious colitis.

4. Bilateral dependent airspace opacities are most compatible with atelectasis, although infectious etiology cannot be completely excluded.

A verbal report was conveyed to Dr Dicks in person.

Resident: Baker, Joe Blunt, MD

I have personally reviewed this study
and agree with the report above.

CTV/JBB Radiologist: Venturini, Chrystel Therese, MD
APPROVED

Print This Page | Close This Window

Name: Jianhua D. Xie | DOB: 9/16/2012 | MRN: 11491118 | PCP: UNLISTED UPIR REQUESTED

ULT ABDOMEN WITH DOPPLER - Details (Jianhua)

Study Result

Impression

IMPRESSION:
1. Findings consistent with hepatic parenchymal disease with multiple diffuse echogenic subcentimeter foci in the liver favored to represent that may represent small venous malformations.
2. Borderline splenomegaly.
3. Normal Doppler study of the liver.

Narrative

CLINICAL HISTORY: Upper abdomen ultrasound to evaluate patient with cirrhosis, pancreatic insufficiency, elevated LFT's. Patient listed for liver transplant in Washington.

COMPARISON: None

PROCEDURE COMMENTS: Ultrasound of the abdomen with Doppler was performed.

FINDINGS:
The liver is echogenic and coarse in echotexture, the contour is mildly nodular. There are multiple subcentimeter echogenic foci diffusely throughout the liver, the largest of which measures 0.7 x 0.6 cm (craniocaudal, AP). The common bile duct measures 0.7 mm. There are no visible gallstones, gallbladder wall thickening or pericholecystic fluid.

The pancreas is diffusely echogenic. The great vessels and both kidneys are visualized and appear normal. The right kidney measures 6.2 cm in length, while the left measures 6.7 cm in length. No abnormal masses or fluid collections are seen.

The spleen is normal in morphology and echogenicity but borderline enlarged measuring 7.9 cm.

Hepatic arterial, hepatic venous and portal venous waveforms are usual in direction and amplitude as documented by both color and spectral Doppler evaluation.

The resistive indices are not reported.

Component Results

There is no component information for this result.

General Information

Collected:	03/04/2015 11:51 AM
Resulted:	03/04/2015 1:23 PM
Ordered By:	Jorge A. Bezerra, M.D.
Result Status:	Final result

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All Orders (03/04/15 - 03/04/15) (continued)

ULT Abdomen With Doppler — Completed

Electronically signed by:	Bezerra, Jorge A., MD 02/19/15 1122, for Ordering in Verbal mode, Communicator - Mitchell, Joanne, RN
Diagnoses:	Cirrhosis of liver without mention of alcohol [571.5]
Questions:	Symptoms, background information, or clinical history? upper abd ultrasound to evaluate patient with cirrhosis, pancreatic insufficiency, elevated LFT's, listed for liver transplant in Washington Reason for request or specific question(s) to be answered evaluate for abnormality Phone Report? No

ULT Abdomen With Doppler — Completed

Ordering user:	Mitchell, Joanne, RN 02/18/15 1714	Ordering provider:	Bezerra, Jorge A., MD
Authorized by:	Bezerra, Jorge A., MD		
Electronically signed by:	Bezerra, Jorge A., MD 02/19/15 1122, for Ordering in Verbal mode, Communicator - Mitchell, Joanne, RN		
Specimen:	03/04/15 1151		
Diagnoses:	Cirrhosis of liver without mention of alcohol [571.5]		
Questions:	Symptoms, background information, or clinical history? upper abd ultrasound to evaluate patient with cirrhosis, pancreatic insufficiency, elevated LFT's, listed for liver transplant in Washington Reason for request or specific question(s) to be answered evaluate for abnormality Phone Report? No		

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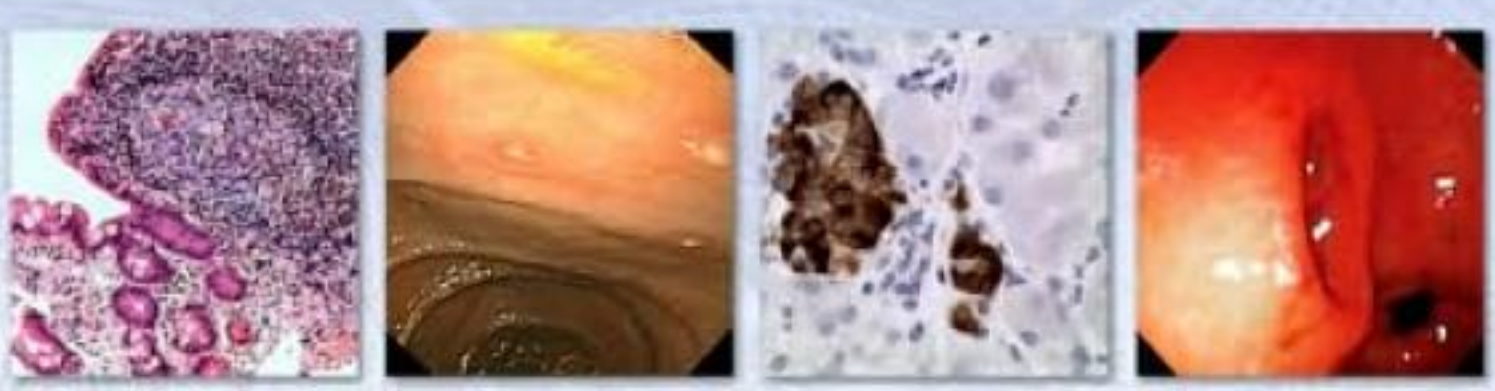
Pediatric Gastrointestinal and Liver Disease



FOURTH EDITION

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classified in the group "autoimmune cholangiopathy." In children, the most problematic diagnostic issue is the distinction between PSC and AIH, with or without concurrent ulcerative colitis.[181,182] Histologic features of either or both may be present, and macroscopic bile ducts may or may not be affected. ANA and/or ASMA may be detected. For this reason, some authors recommend cholangiography in children who present with hepatitis, Hypergammaglobulinemia, and autoantibodies.

Treatment

Chronic AIH generally responds to immunosuppressive therapy, of which corticosteroids have become the mainstay. Immunosuppressive therapy for AIH can be divided into two phases: (1) induction of remission and (2) maintenance of remission. There are no widely accepted guidelines for initial dosage and withdrawal of immunosuppressive agents. One pediatric regimen begins with prednisolone, 2 mg/kg/day (maximum 60 mg) and is gradually decreased over a period of 4 to 6 weeks to the minimum dose capable of maintaining normal aminotransferase levels.[185] If excessive doses of corticosteroids are required to maintain normal aminotransferase levels or if the child does not achieve remission, then azathioprine at a dose of 0.5 mg/kg/day is started. Based on the patient's response and presence or lack of drug-induced toxicity, the dose of azathioprine may be increased to 2 mg/kg/day. 6-Mercaptopurine, a related purine analogue, can be substituted for azathioprine at a lower dose and, in some cases, has facilitated induction of remission when azathioprine has failed.[199] Results of this treatment protocol are shown in Table 75-9. The time necessary to achieve normalization of aminotransferases can be prolonged. In this protocol, normalization was reached after a median of 0.5 year (range, 0.2 to 7) in AIH-I and 0.8 year (range, 0.2 to 3.2) in AIH-II.[185]

Immunosuppressive therapy may be withdrawn in some patients, allowing a prolonged "disease-free" period. This is usually attempted when a liver biopsy shows minimal or no inflammatory changes after at least 1 year of normal aminotransferases. Withdrawal of therapy is preferably not attempted during or after puberty and within 3 years of diagnosis.[200] Most children will require indefinite chronic, low-maintenance doses of corticosteroids and a purine analogue, alone or in combination, to maintain remission. Alternate-day or pulsed corticosteroid regimens have been disappointing.[180]

Forty percent of children will have at least one episode of relapse while on treatment, and many will progress to cirrhosis.[185] The risk of relapse is greater if prednisone is administered on alternate days. Poor indicators of response to therapy include cirrhosis at initial biopsy, diagnosis at a young age, long duration of disease, and presence of the HLA-B8 or DR3 phenotype.[180] Empiric nonsteroidal treatments including ursodeoxycholic acid, cyclosporine, methotrexate, mycophenolate mofetil, and tacrolimus have been used in limited studies to treat recalcitrant disease or corticosteroid intolerance.

Of alternative agents, the greatest experience to date has been with cyclosporine. A pilot, multinational, multicenter, clinical trial of cyclosporine involving 32 children with autoimmune hepatitis was published in 1999.[201] Cyclosporine was administered alone for 6 months, followed by combined low doses of prednisone and azathioprine for 1 month, after which cyclosporine was discontinued. Of 30 patients, ALT levels normalized in 25 by 6 months and all had normal levels by 1 year of treatment. Longer-term follow-up (median 29 months) of 84 children on the same protocol revealed normalization of aminotransferases in 94% of patients, with remission obtained in 79% of patients at 7 months. The presence of both hyperbilirubinemia and portal hypertension at diagnosis were predictors of delay in remission.[202]

Limited data are available regarding other therapies. In some children with refractory AIH there seems to be a role for mycophenolate mofetil (MMF).[203,204] Budesonide, a synthetic glucocorticoid with a high first-pass metabolism by the liver, has been used with some success in a few cases,[205-207] but discordant results have also been published.[208]

Patients with AIH who have failed medical therapy or who presented initially with end-stage liver disease have been referred for liver transplantation with success. The disease may recur after transplantation despite aggressive immunosuppression or several years after grafting when immunosuppression is reduced.[180] Although liver transplantation may be undertaken in children with AIH, the recurrence rate is higher than that reported in adults,[209] and recurrence does not always respond to treatment. In addition, *de novo* AIH is sometimes seen in children after liver transplantation for an unrelated disease.

NONALCOHOLIC FATTY LIVER DISEASE

Introduction and Definitions

The epidemic of obesity in adults, children, and adolescents has many significant consequences for the health of the population. The high prevalence of obesity has led to the recognition and characterization of types of chronic liver disease previously thought to be uncommon and limited to selected adult patients. This group of disorders is called nonalcoholic fatty liver disease (NAFLD) when alcohol is excluded as the etiology. NAFLD is increasingly recognized in children and adolescents and has become the most common form of chronic liver disease in this population. Fatty liver, also referred to as hepatic steatosis, refers to accumulation of fat in the parenchymal cells of the liver. NAFLD represents a spectrum of types and severity of hepatic steatosis. When the steatosis is accompanied by necroinflammation and varying degrees of fibrosis, this more severe form of the disease is called nonalcoholic steatohepatitis (NASH). NAFLD should be distinguished from microvesicular steatosis of the liver, which is seen in a variety of inherited or acquired disorders that have a final common pathway of defective oxidation of free fatty acids. NAFLD is a histologic diagnosis: it may be associated with or caused by a variety of underlying diseases or drugs (Table 75-10). Progression of NASH to chronic liver disease with significant fibrosis and cirrhosis is well documented. NASH is now thought to be responsible for much of the noninfectious end-stage liver disease in the United States.

Histologic Features

Although liver biopsy may not be indicated in every child who is obese, has abnormal aminotransferases, and shows clinical evidence of insulin resistance (see later discussion), histology is required for the definitive diagnosis of NAFLD. Once the histologic lesion has gone beyond simple steatosis, the liver disease is classified as NASH. The primary defining features of NASH in adults include macrovesicular steatosis, parenchymal lymphocyte-predominant inflammation, and ballooning hepatocyte degeneration (Figure 75-9). Other features observed with variable frequency include perisinusoidal fibrosis (predominantly in zone 3, the hepatocytes around the central veins), Mallory's

TABLE 75-10. **Causes of NAFLD and NASH**

Acquired metabolic conditions
Obesity
Diabetes mellitus
Rapid weight loss
Total parenteral nutrition
Acute starvation
Genetic metabolic conditions
Wilson's disease
Hereditary tyrosinemia
Abetalipoproteinemia
Surgical procedures
Jejunoileal bypass
Gastroplasty
Extensive small bowel resection
Drugs/toxins
Glucocorticoids
Amiodarone
Synthetic estrogens
Isoniazid
Others
Miscellaneous
Small bowel bacterial overgrowth

Adapted from Reid AE. Nonalcoholic steatohepatitis. Gastroenterology 2001; 121:710-723. Copyright 2001 AGA.

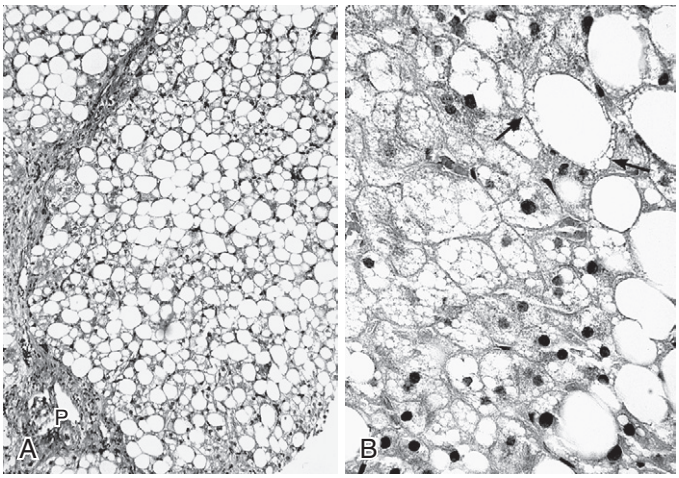

Figure 75-9. Histologic findings in NAFLD. Photomicrograph of the liver in NASH. (**A**) At low power, large lipid droplets can be seen in many of the enlarged hepatocytes. Bridging fibrosis and some inflammation in the portal areas are also noted. (**B**) At higher magnification, the large lipid vacuoles are seen to be compressing the cellular organelles and nuclei to the periphery of the hepatocytes (arrows).

hyaline, glycogenated nuclei, lipogranulomas, steatonecrosis, and iron accumulation. These findings in children are designated as "type1" NASH. "Type2" NASH, which is more common in children, is characterized by macrovesicular steatosis with portal inflammation and/or fibrosis, generally without lobular inflammation. Children with advanced fibrosis tend to have the "type 2" NASH pattern and to be younger and more obese.[210] It is not known whether the pattern of NASH evolves as children grow.

The extent of fibrosis varies considerably, but fibrosis has been found in a higher prevalence of pediatric patients with NASH at presentation, compared with adults.[211] Well-established cirrhosis is found on initial biopsies in 7 to 16% of adult patients with NASH.

Prevalence and Risk Factors

The prevalence of NAFLD in the general population is not known because the majority of affected individuals are asymptomatic and there is no reliable surrogate screening. Autopsy studies and studies of general populations have demonstrated rates of approximately 20% for NAFLD and 2 to 3% for NASH, but rates are substantially higher in obese and diabetic subjects. In a study of nonalcoholic adult patients referred for evaluation of abnormal aminotransferases, in whom no other etiology could be identified, NASH was found at biopsy in 26%.[212]

Prevalence rates for children and adolescents are not available because there are no large series of liver biopsies for abnormal aminotransferase values. However, an estimate of the magnitude of NAFLD in childhood was made from data gathered in the NHANES cycle III database (1988-1994).[213] Abnormal ALT values were noted in 1.5% of adolescents of normal weight, in 5% of the overweight, and in 9.5% of the obese. When children referred to obesity programs are studied, the prevalence of ALT abnormality increases to 12 to 25%, and the presence of fatty liver increases to 53%.[214] A children's autopsy study in the United States revealed the overall prevalence of NAFLD to be 9.6%, increasing with age (0.7% for ages 2 to 4 years versus17.3% for ages 15 to 19 years).[215]

Risk factors for NAFLD in adults include obesity, type 2 diabetes mellitus, dyslipidemia, and metabolic syndrome. In the pediatric study, the most prominent risk factor for NAFLD was obesity (38%), but race was also a strong predictor, with Hispanics having the highest risk and African Americans having the lowest.[215] In all reports of NAFLD in children, boys outnumber girls in a 2:1 ratio.[216]

Pathogenesis

The pathogenesis of NAFLD has not been completely elucidated. Fat deposition in the liver occurs when the degree of lipogenesis is greater than the rate of lipolysis. This may result from delivery of fatty acids to the liver in greater amounts than is needed for the processes of mitochondrial oxidation for energy and synthesis of necessary lipids and phospholipids. This mechanism might explain the hepatic steatosis in obesity, acute starvation, excessive dietary fat intake, and total parenteral nutrition. Alternatively, decreased use of fatty acids within the liver, by either disturbed mitochondrial oxidation or decreased synthesis, might also cause fat accumulation.

It is becoming clear that insulin resistance is a critical factor in the generation of NAFLD. Insulin promotes retention of triglyceride in hepatocytes. It has been demonstrated repeatedly that most patients with NAFLD or NASH have raised insulin levels or insulin resistance even in the absence of obesity or hyperglycemia. This association has been noted in children as well.[217]

The first inciting factor in the development of NAFLD and NASH is the accumulation of triglycerides in hepatocytes. It is now generally accepted that a "second hit" is necessary once hepatic steatosis is established, to promote progression to hepatocellular injury associated with inflammation and then fibrosis (Figure 75-10). The resultant hepatocyte damage may then stimulate the influx of inflammatory cells, initiating an inflammatory cytokine cascade and leading to further tissue injury.

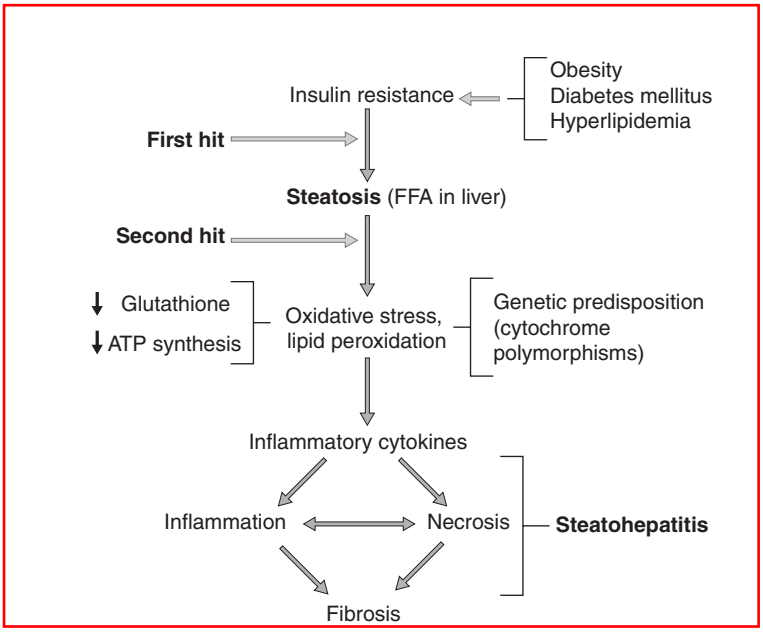

Figure 75-10. Two-hit hypothesis of NASH. Current understanding of the pathogenesis of hepatic steatosis and NASH. Insulin resistance associated with a variety of conditions causes accumulation of free fatty acids in hepatocytes, the "first hit" of hepatic steatosis. A "second hit" injury caused by or associated with steatosis and mediated through lipid peroxidation causes release of inflammatory cytokines. The resultant inflammation and cell necrosis stimulate fibrogenesis, leading to the full-blown picture of steatohepatitis.

Clinical Features

NAFLD and NASH are asymptomatic in the majority of patients. Symptoms such as fatigue, malaise, and vague right-upper-quadrant pain may be more common in adolescents. In most patients, NAFLD is discovered when hepatomegaly or abnormal ALT concentration is detected on routine testing or evaluation for another problem. Hepatomegaly, although sometimes difficult to appreciate owing to obesity, is present frequently, and not all patients have abnormal ALT values. Obese young adults with a high degree of abdominal-wall fat are more likely to have NAFLD. Acanthosis nigricans, commonly found on the neck and axillae of children and adolescents with insulin resistance, is found in 50% of children with NASH.[217,218] Ultrasonography may reveal a granular-appearing, echogenic liver that is difficult to penetrate.

Laboratory findings in NAFLD and NASH are nonspecific. Typically, AST and ALT levels are increased two- to fivefold, although higher levels are sometimes seen. The ALT is usually higher than the AST value. Some children have hyperlipidemia. Bilirubin, albumin, and prothrombin time values are normal until the very latest stages of disease.

Natural History

The natural history of pediatric NAFLD is unknown. Hepatic steatosis alone may have a benign or indolent course for many years. Once inflammation and tissue damage develop, progressive liver disease often ensues. In particular, the findings of inflammatory infiltrates and hepatocyte balloon degeneration suggest a high likelihood of progression to fibrosis and cirrhosis.[219]

The frequency with which NASH progresses to end-stage liver disease is unknown. A population based study in the United States found that NAFLD patients had a slightly higher mortality than the general population, associated with advanced age, impaired fasting glucose, and cirrhosis.[220] Similar results were reported in a more recent study.[221] In pediatrics there are no published longitudinal outcome studies of NAFLD. However, instances of advanced liver disease and cirrhosis have been described during childhood and adolescence.[222,223] NAFLD and NASH must be recognized as potential causes of serious liver disease in this population.

Treatment

All overweight or obese children and adolescents should undergo ALT testing and physical examination for hepatomegaly. Those with abnormalities should undergo diagnostic testing to exclude other causes of liver disease. If none is found, a trial of weight loss should be recommended; if successful, and ALT becomes normal, then perhaps no intervention is warranted. If unsuccessful, or if signs of more advanced liver disease are present, abdominal imaging and liver biopsy should be considered. The optimal treatment for NAFLD and NASH has not been determined. Treatment may not be necessary for simple steatosis because the natural history is benign, but at least from preliminary data it seems that most children and adolescents with fatty liver have some inflammation and fibrosis. It is important to determine, even in overweight children, if the steatohepatitis is secondary to another liver disease, such as Wilson's disease, chronic hepatitis C, inborn errors of metabolism, or hepatotoxic medications, because specific therapies are available.

Treatment may be directed at the underlying medical condition, if possible. Improvement in ALT levels and hepatic histopathology has been described with weight reduction in obese individuals. In a series of 33 obese children with NAFLD, liver tests became normal in all children who lost weight on a restricted calorie and exercise regimen, and ultrasonographic findings of hepatic steatosis improved significantly or normalized in children who lost at least 10% of body weight.[214] The optimal rate and degree of weight loss for improvement in hepatic histology has not been established. Therapy aimed at treatment of underlying diabetes mellitus or hyperlipidemia, common coexisting disorders with obesity, may be helpful in overall patient health, but efficacy in treatment of NAFLD has not been proven.

Pharmacologic therapies that have been attempted for NAFLD or NASH include ursodeoxycholic acid,[224] lipid lowering agents (clofibrate, gemfibrozil), betaine,[225] *N*-acetylcysteine, vitamin E,[226] and insulin-sensitizing agents (metformin,[227] thiazolidinediones[228]). Currently there are no conclusive data to support the use of pharmacological therapies for NAFLD in children, and it is advised only in the context of clinical trials.

At a minimum, it seems prudent to advise lifestyle changes achieved through diet and regular physical activity, and, in those with significant insulin resistance or diabetes mellitus, insulin-sensitizing agents may be considered.

TREATMENT OF HEPATITIS

Treatment of Acute Hepatitis

Acute-Phase Supportive Care

General supportive measures for acute hepatitis include adequate rest and diet, although these have not been studied in children. It is reasonable to advocate a balanced diet that

prevents weight loss, dehydration, and nutritional deficiencies. Strict bed rest is generally not required, but permitted levels of activity should take into account the child's general condition. The return to normal activities and school requires knowledge of the child's clinical status, the type of hepatitis (including mode of transmission and duration of infectivity), and local health regulations. For example, most school-age children with acute HBV infection can return to school as soon as they are physically able because they pose little threat of transmission.[229] Young children with HAV infection, regardless of their general condition, however, should not return to day-care centers until their period of viral shedding has ended, which is 1 week after the onset of symptoms.[30]

Measures must also be undertaken to reduce the risk of spread of infectious hepatitis during the period of infectivity. These include education directed toward the child's caregivers and contacts, reporting to local health authorities when required, and active and passive immunization when indicated. Appropriate follow-up should confirm resolution.

Antiviral Therapy

With the exception of acute hepatitis C, antiviral therapy is not recommended for the treatment of acute hepatitis in immunocompetent hosts. Treatment has been advocated for immunocompromised children with acute hepatitis due to EBV or CMV infection. Acyclovir and ganciclovir have been used for the treatment of EBV infection, but only in the active and not the latent phase of infection. The antiviral effect of ganciclovir for EBV is believed to be more prolonged after withdrawal than that of acyclovir.[230] Ganciclovir has been used with success in newborns and immunocompromised children with active CMV. Induction therapy for 2 to 3 weeks is usually followed by prolonged maintenance therapy because viral excretion most usually recurs on cessation. CMV immune globulin derived from pooled plasma from adults selected for high CMV antibody titers has also been used in conjunction with an antiviral agent.

Treatment of Chronic Hepatitis

Chronic-Phase Supportive Care

Supportive care for the child with chronic hepatitis involves maintenance of long-term well-being, monitoring for the complications of chronic liver disease, and avoidance of any further hepatic injury. Many children with chronic hepatitis are diagnosed fortuitously and are asymptomatic. In these children there are no restrictions to activity and they may lead normal lives. Some children with stable disease and mild symptoms such as fatigue or poor appetite will require interventions commensurate with their disability, to maintain nutritional status and normal schooling. Other children, such as those with chronic AIH, may have labile disease, with frequent "flares" separated by disease-free periods of variable duration. These children will require early recognition of relapses with appropriate modification of therapy. Patients with advanced disease and manifestations such as ascites or coagulopathy require aggressive therapy directed at the specific sequelae of long-term liver disease.

Children with chronic hepatitis should avoid chronic high dosages of potentially hepatotoxic medications to avoid further aggravation of liver injury and should be immunized against hepatitis A and B if their serologic tests do not reveal adequate immunity. Exposure to all environmental hepatotoxic agents (e.g., organophosphates) should be avoided.

Specific therapies for the various type of chronic hepatitis have been discussed.

SUMMARY

Over the past 2 decades, much has been learned about childhood hepatitis. Early intervention in childhood may significantly improve longevity. Effective treatment regimens are available for HBV and HCV, and NAFLD has gained prominence as a major potential cause of morbidity. New directions for research include elucidation of appropriate patient selection for treatment, clinical trials of newer agents in children, and exploration of the molecular basis of liver injury in the various causes of hepatitis.

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See expertconsult.com for a complete list of references and the review questions for this chapter.

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Hematology Consultation

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HEMATOLOGY CONSULTATION

XIE, JIANHUA DRACO
DOB: 09/16/2012 M -MR #: 01-27-55-67

DATE OF ADMISSION: 04/09/2013 DATE OF CONSULTATION: 04/11/2013

IDENTIFICATION: We were asked by Dr. Lincoln Smith to evaluate this 6-month-old male, previously healthy, with regards to his most recent findings on CT of liver lesions and possible infiltrative process to evaluate for malignancy.

HISTORY OF PRESENT ILLNESS: Patient is a 6-month-old male with no significant past medical history who was healthy until approximately 1 week ago when parents noticed increasing loose stools which significantly increased on Sunday (5 days ago) and then over the following 2 days they noticed worsening generalized edema and jaundice. He presented to his pediatrician on Tuesday, 4/9, and were promptly sent to at Seattle Children's Emergency Room. In the emergency room, he was febrile, T-max of 40 degrees Celsius. Blood cultures were drawn and he was given a dose of ceftriaxone. He did have 1 episode of nonbloody, nonbilious emesis and received normal saline boluses for fluid resuscitation. Laboratory values at that time demonstrated coagulopathy with an INR of 5.6, hyperbilirubinemia, and a mild transaminitis. He was transferred to the ICU for further evaluation and treatment of his coagulopathy as well as close monitoring. He underwent ultrasound of the abdomen and CT of the chest, abdomen and pelvis today which prompted the consultation.

REVIEW OF SYSTEMS: Parents deny any weight loss or recent fevers other than the fever in the emergency room. A 5-day history of diffuse edema and jaundice and intermittent but progressively worsening loose stools was reported. Loose stools were yellow, he did have emesis in the emergency room, which was nonbloody, nonbilious. He has otherwise been active and developing well. Parents deny any unusual lymphadenopathy, skin rashes, bruising, scleral icterus, weight loss, failure to gain weight, loss of milestones.

Per her parents, patient has been otherwise well. He was diagnosed with RSV (respiratory syncytial virus) infection in January but did not require hospitalization. He has had frequent loose stools for most of his life requiring change in formulas but has continued to grow and develop well.

PAST MEDICAL HISTORY: Patient was born 10 days prior to his due date. Pregnancy was uncomplicated. His formula was converted from a milk-based formula to a soy-based formula at approximately 2 months of age. As stated, he had an RSV (respiratory syncytial virus) infection in January, not requiring hospitalization. He has been growing and developing well.

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SOCIAL HISTORY: Parents live at home, mother, father, and 3 siblings, all of whom are currently healthy. He has not had recent travel exposure.

FAMILY MEDICAL HISTORY: Father does report approximately 1 week ago he did have what seemed to be gastroenteritis with diarrhea which resolved over 2 days. Mom has a history of "low platelets" though she has never had any bleeding or bruising difficulties. His older brother did have an episode of thrombocytopenia last October following a viral illness which did not require any therapies nor hospitalization and has since resolved. His other siblings are healthy. There is a history of a maternal grandfather with pancreatic cancer, developed in his 60s. No other maternal family history. Paternal family history is unknown as per dad his family lives in a small town without healthcare in China and many adult family members die young. However, there is not a history of childhood deaths.

MEDICATIONS:
Albuterol as needed for wheezing
Piperacillin/tazobactam 945 mg q.8h.

ALLERGIES: No known drug allergies.

ADMISSION PHYSICAL EXAMINATION:
Temperature 36.3, heart rate 110, respiratory rate 34, oxygen saturations 100, blood pressure 77/30.
General: Patient is in no acute distress.
HEENT: Sclerae are anicteric. Moist mucous membranes. No nasal congestion. No appreciable cervical lymphadenopathy. Patient is intubated with the ET-tube in his mouth. I cannot fully examine his intraoral cavity.
Chest: Clear to auscultation bilaterally.
Cardiovascular: 2/6 systolic murmur heard at the left sternal border. S1, S2, regular rate and rhythm.
Abdomen: Protuberant with fluid wave, reducible umbilical hernia. Liver edge approximately 3 cm below the costal margin, spleen 2-3 cm below the costal margin.
Extremities are edematous. 2+ pulses throughout.
Lymphatics: no appreciable lymphadenopathy

LABORATORY DATA:
4/9: Blood gas pH of 7.43, CO2 of 23, oxygen of 135, bicarbonate of 14.8. Sodium 135, potassium 5.2, glucose 120, ionized calcium 1.27, lactic acid 3.1 at 8:30, at 10:15 lactic acid was 2.1, CRP less than 0.8, amylase and lipase less than 30 and less than 10, GGT 54.
Rhinovirus positive.
White blood count 27, hematocrit 24.8, platelets 146, ANC 20250, no blasts.
4/10: PTT 48.6, INR 5.6, PTT 75, fibrinogen 60, total protein 4.1, ionized calcium 1.15, ferritin 93, conjugated bilirubin of 4.0, unconjugated 10.3, AST 107, ALT 91, alkaline phosphatase 1270, triglycerides 47, albumin 2.3, LDH 810
Hepatitis A IgM nonreactive, hepatitis A total antibody reactive, CMV (cytomegalovirus) negative, EBV (Epstein-Barr virus) negative. Parvo negative. CMV IgG positive, IgM negative, EBV IgG positive, IgM
Tylenol level less than 10
Alpha-fetoprotein 7080, ammonia 40. negative.

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4/11: Total bilirubin 11.1, conjugated 3.5, unconjugated 6.7, AST 94, ALT 84, alkaline phosphatase 10, 67, ammonia 43, lactic acid 0.9, albumin level 2.0.

IMAGING:
4/9 at 11:48 p.m.: Abdominal ultrasound: Mild intraperitoneal free fluid. Mild diffuse gallbladder wall thickening with cholelithiasis and pericholecystic fluid, likely related to volume overload, third spacing, mild hepatomegaly, trace bilateral pelviectasis.
Ultrasound 4/10 at 10:30 in the morning: Edematous-appearing liver with interval development of multiple small echogenic foci throughout the right lobe of the liver. The latter findings suggesting a diffuse inflammatory etiology including septic emboli, persistent splenomegaly, contracted gallbladder, likely reflecting nonfasting state, trace central pelviectasis of the right kidney, small amount of anechoic fluid and peritoneal fluid, abnormally elevated resistive indices measuring 1.0 throughout the liver, recanalization patency of the umbilical vein in conjunction with splenomegaly suggestive of portal hypertension.

CT of the chest, abdomen and pelvis: Diffuse hazy mesentery which could represent edema in the setting of portal hypotension including recanalization of the paraumbilical vein, minimal gastric varices and moderate splenomegaly as well as diffuse subcutaneous edema, numerous small hypodense hepatic lesion too small to further characterize, and intermediate fatty density is seen within several lesions. Sigmoid colon and rectal wall thickening of mucosal hyperenhancement, bilateral dependent air space opacities.

ASSESSMENT AND PLAN: 6 month old male with diffuse anasarca, hyperbilirubinemia, coagulopathy, anemia, thrombocytopenia and leukocytosis suggestive of acute hepatic failure and unlikely to be due to an underlying oncologic process.

Oncologic hepatic infiltrative processes do occur. There are cases reported in the literature of acute liver failure due to leukemia. However, I would expect that the patient would be pancytopenic and he does have a robust neutrophil count which leads us away from the diagnosis of leukemia. Given the patient's coagulopathy and the low suspicion for leukemia we do not recommend a bone marrow evaluation at this time. Neuroblastoma can infiltrate the hepatic tissue and I would recommend sending VMA/HVA labs. I am reassured that we have a CT scan of the chest, abdomen and pelvis which does not reveal any masses that would represent a primary lesion. Lymphoma can metastasize to the liver but typically presents with other mass lesions and the liver lesions develop over time (the patient's liver lesions developed over a 10 hour period early in admission). Finally, primary hepatic neoplasms, such as hepatoblastoma, are typically large masses and, again, do not develop over a period of hours. We feel the liver failure is likely due to an isolated hepatic process and much less likely an oncologic process. We do not recommend further evaluation for a neoplasm at this time.

Thank you for the very interesting consult. Please do not hesitate to contact us with any questions or concerns.Attending Statement: For this visit I have seen and evaluated this patient, reviewed the history, exam and plan with the resident/fellow. I agree with the note and plan of care as documented above.

Edited and Electronically Authenticated by
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CNS/clw Doc #2934232 d: 04/11/2013 09:44 P t: 04/11/2013 10:52 P (1555889-)
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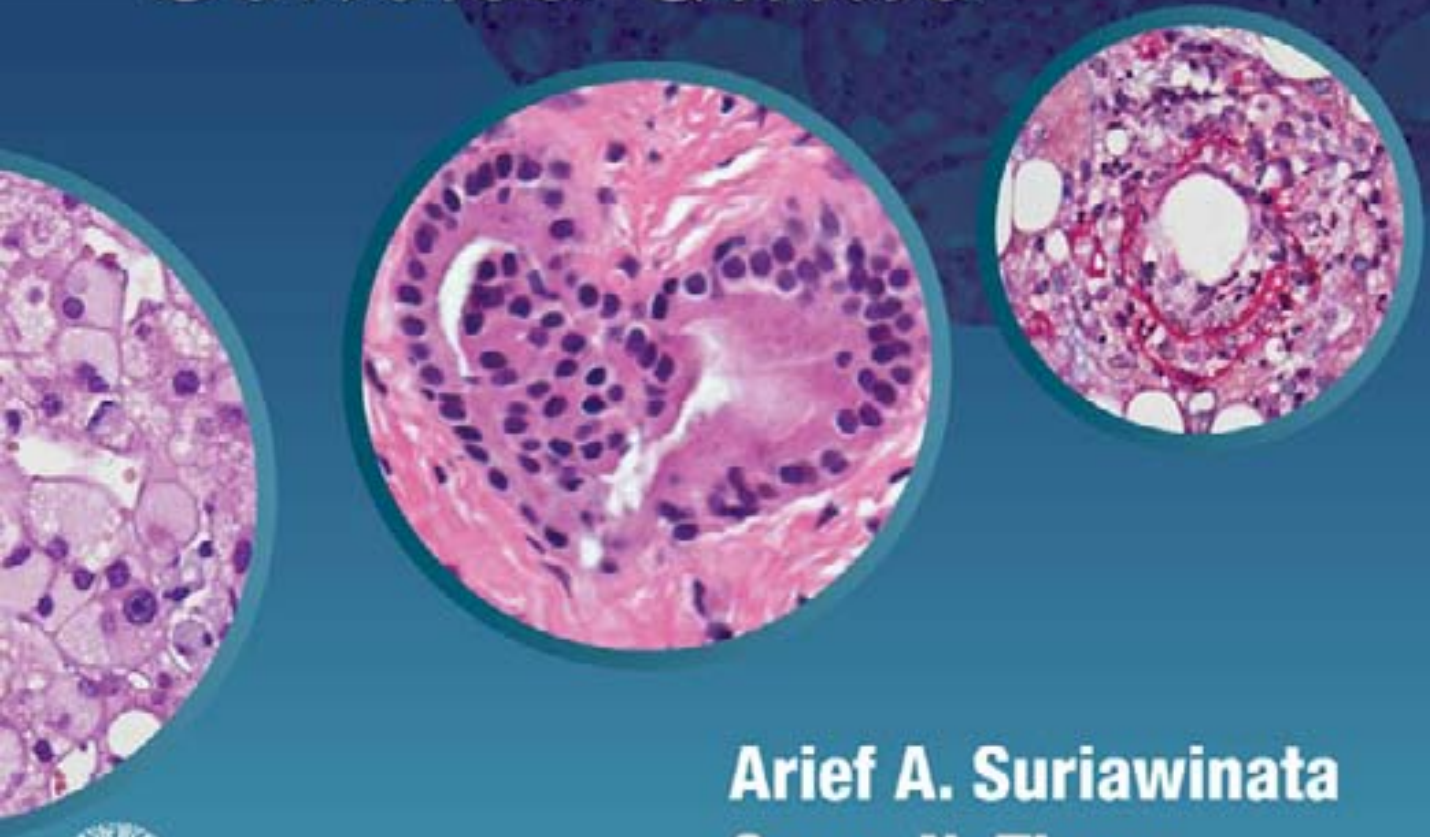
Julie E Wen, MD

Liver Pathology

An Atlas and Concise Guide



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1.6 Hepatocyte Degeneration, Death, and Regeneration

Normal liver structure and function depends on the balance between hepatocyte death and regeneration. A limited minor hepatocyte injury results in immediate regeneration of the hepatocytes without significant or prolonged effect in the liver structure and function, whereas a severe acute hepatocyte injury may exceed the regenerative capacity of the hepatocytes and results in parenchymal collapse and liver failure.

Hepatocyte Degeneration and Death

Two types of hepatocyte death can be distinguished by morphologic features: (1) apoptosis and (2) cytolytic necrosis. It is likely, however, that these are two ends of a spectrum with possible intermediate forms.

Apoptosis involves shrinkage, nuclear disassembly and fragmentation of the cell into discrete acidophilic bodies with intact plasma membranes, which are then rapidly phagocytosed by neighboring Kupffer cells (Figure 1.6.2).

In cytolytic necrosis, the process begins with ballooning degeneration where hepatocytes become swollen, rounded, and pale staining as a result mainly from dilation of the endoplasmic reticulum, which is the consequence of mitochondrial dysfunction and ATP depletion, leading to the loss of ion homeostasis and plasma membrane integrity. The cytoplasm is partially rarefied, particularly along the cellular periphery, and the cytoplasmic cytoskeleton clumps around the nucleus; cell membranes are frequently indistinct (Figure 1.6.1). Ballooned hepatocytes undergo lytic necrosis, which is not visible, but the occurrence can be inferred to small foci of stromal collapse that are accompanied by collections of lymphocytes and Kupffer cells (Figure 1.6.4), referred to as spotty necrosis. The degree of ballooning degeneration varies across the lobule in hepatocellular injury, although classically, the centrilobular region is the most severely affected.

Hepatocyte Regeneration

The liver is the only human organ that is capable of natural regeneration. Regeneration may be rapid as seen after partial hepatectomy. This is predominantly due to the hepatocytes reentering the cell cycle: quiescent cells stimulated by mediators, including cytokines, move into a primed state (G0 to G1) when growth factors can stimulate DNA synthesis and cellular replication.

In the event of injury, regeneration is observed predominantly in the periportal hepatocytes in mild injury or throughout the hepatic parenchyma in severe injury. It is manifested by mitoses, multinucleation, and crowding of the periportal cell plates by small, uniform, clear, or basophilic hepatocytes (Figure 1.6.5). Liver cell plates in the periportal region become irregularly thickened, and occasional hepatocellular rosettes may appear. Nuclear displacement to the sinusoidal pole with hyperchromasia is a cytologic indication of regenerative activity. All of these changes impart a darkened periportal region under low magnification, which is often the only remarkable change in mild acute hepatitis or in residual hepatitis as a reaction to recent injury. In severe hepatocellular injury or hepatitis, the feature of regeneration may be overwhelmed by the amount of ballooning degeneration, cytolytic necrosis, apoptosis, bridging necrosis, and inflammatory infiltrate.

The degree of hepatocyte regeneration often correlates with the degree of necroinflammatory activity in chronic hepatitis, particularly when interface hepatitis is the predominant process. Similarly, hepatocyte regeneration occurs in the periphery or periseptal region of cirrhotic nodules when the necroinflammatory activity persists, resulting in regenerative nodules in cirrhosis.

If hepatocytes are extensively damaged, such as in massive hepatic necrosis, the conventional hepatocyte regeneration is impaired. Hepatocytes may be derived from bipotential stem cells, so-called oval cells, which are thought to rest in the canals of Hering. These cells can differentiate into either hepatocytes or cholangiocytes.