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10 CHAPTER

Liver and Bile Duct Infections

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The liver is the target of many infectious agents, most notably hepatotropic viruses such as hepatitis B virus (HBV) and hepatitis C virus (HCV). Additionally, many infectious organisms can involve the liver in the setting of disseminated infection, in immune-suppressed patients, or as a medical curiosity. The major challenge facing the pathologist in diagnosing these conditions is that many of these diseases have overlapping histopathologic characteristics. Hepatitis, necrosis, or granulomas are characteristic of many liver infections, and distinguishing the exact cause often requires a meticulous search for organisms, attention to subtle morphologic clues, or, not uncommonly, clinical, epidemiologic, or serologic data. Although some organisms can be readily detected in tissue, many are not, even with the use of ancillary techniques. Furthermore, many of the ancillary techniques used to detect organisms in tissue are not widely available. Therefore, although the pattern of injury can provide a differential diagnosis, in some cases, the final diagnosis relies on culture or serologic studies.

Viruses

Hepatitis A

Hepatitis A virus (HAV) is an RNA virus in the Picornaviridae family. Although the incidence of HAV infection has fallen dramatically since the introduction of vaccines, it still causes approximately 60,000 infections per year and occasionally causes dramatic outbreaks with fulminant hepatitis and death.[1] Fecal-oral transmission is facilitated by extensive viral shedding in feces during the 3- to 6-week incubation period, which reaches a maximum just before the onset of hepatocellular injury.[1] An increasing incidence has been noted among urban homosexual men. An effective vaccine has been developed.

The signs and symptoms of hepatitis A are related to patient age. In children younger than 3 years of age, more than 80% of infections are clinically silent, whereas in adolescents and adults, more than 75% of cases are symptomatic.[2] Symptoms include fever, malaise, abdominal pain, and jaundice. Marked transaminase elevations are characteristic. About 100 cases of HAV-related fulminant liver failure are reported each year, predominantly in adults.[2] Chronic infection does not occur. However, HAV infection can precipitate autoimmune hepatitis, which can progress to chronic hepatitis with fibrosis or cirrhosis.[3-6]

Liver injury in HAV infection is the result of an immunopathologic response to infected hepatocytes rather than a direct cytopathic effect of the virus.[1] The adaptive immune response is highly effective in eliminating the virus. The earliest antibody response is largely that of immunoglobulin M (IgM), with IgG production beginning shortly thereafter; therefore, the diagnosis is established by the detection of anti-HAV IgM (with or without IgG). Anti-HAV IgG persists for life and confers protection against reinfection.[1]

Acute HAV infection may be indistinguishable from other acute viral hepatitides (see discussion of hepatitis B). However, portal plasma cell infiltrates and periportal necrosis may be prominent, causing confusion with autoimmune hepatitis (Fig. 10-1).[7] In rare cases, perivenular cholestasis with relatively little inflammation mimics cholestatic drug reactions. Fibrin ring granulomas have been reported.[8,9]

Hepatitis B

Chronic hepatitis B affects an estimated 400 million persons worldwide, of whom 1 million die annually.[10,11] Three quarters of patients with chronic hepatitis B in the world are Chinese, and sub-Saharan Africa also has high prevalence.[11] In the United States, the incidence of newly acquired HBV infection has been declining due to screening of pregnant women, vaccination, and safer injection practices.[10]

Virology

HBV is a DNA-containing virus with four overlapping open reading frames.[12] Its four genes are core, surface, X, and polymerase genes. The core gene encodes the core nucleocapsid protein, which is important in viral packaging, and hepatitis B

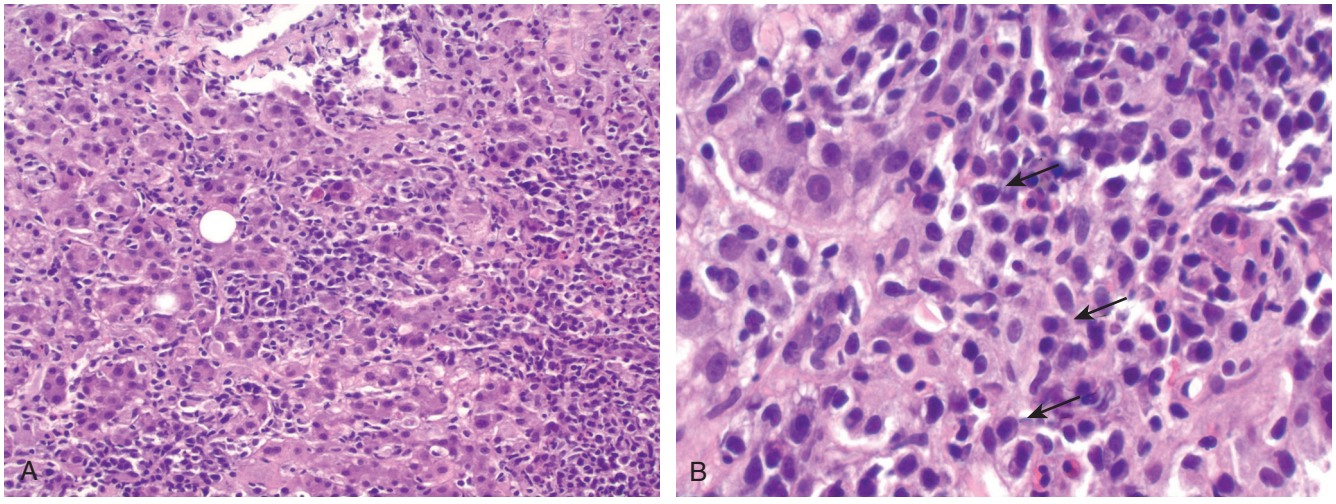

Figure 10-1. Liver biopsy in hepatitis A. **A,** Panlobular inflammation and lobular disarray. **B,** High power shows many plasma cells within the infiltrate *(arrows).*

early antigen (HBeAg). The surface gene encodes pre-S1, pre-S2, and S protein, which are large, middle, and small surface proteins, respectively. The X gene encodes the X protein, which may be important in carcinogenesis. The polymerase gene encodes a large protein that has a role in packaging and DNA replication.[12]

There are eight major HBV genotypes: A is pandemic; B and C are found in Asia, D in southern Europe, E in Africa, F in the United States and South America, G in the United States and France, and H in South America.[11] To some extent, genotype influences the severity of hepatitis and its outcome. The severity of chronic hepatitis is greater with genotype C than with B, and there is a higher frequency of cirrhosis and hepatocellular carcinoma (HCC) in patients infected with HBV genotype C. A higher rate of virologic response is achieved among patients infected with genotype B, compared with genotype C.[13]

Pathophysiology

Hepatitis B is not directly cytotoxic to hepatocytes. Instead, the pathogenesis of HBV infection is related to the host immune response to viral infection. More rigorous immune responses cause more severe liver injury. Patients with a vigorous immune response may suffer fulminant infection with severe liver injury followed by rapid viral clearance, whereas hosts with less vigorous immune responses may become asymptomatic carriers.[10]

Natural History

Transmission of HBV is parenteral. In developed countries, sexual contact, intravenous drug use, acupuncture, and transfusion constitute the most common modes of transmission. In developing countries, vertical transmission is more significant.

Acute hepatitis B manifests as an icteric illness after an incubation period of 6 weeks to 6 months in up to 50% of infected persons.[10] A subset of patients experience a prodromal phase characterized by arthralgias and urticarial skin rash.[14] Acute infection is diagnosed by the detection of hepatitis B surface antigen (HBsAg), IgM antibodies to hepatitis B core antigen (anti-HBcAg), and HBeAg. The outcome of acute hepatitis depends on the immune status and age of the host. Chronic HBV infection develops in as many as 90% of neonates and infants but in only 1% to 5% of immunocompetent adults.[10,11] Patients with chronic HBV infection rarely have extrahepatic manifestations, such as polyarteritis nodosa or glomerulonephritis.[14] Many remain asymptomatic until they present with cirrhosis, HCC, or both.

The presence of HBsAg in serum for 6 months or longer is indicative of chronic HBV infection. Chronic HBV infection manifests in one of several well-defined stages. The immune tolerance phase is seen largely in patients who acquire infection at birth or in early childhood. These patients have high levels of HBV replication but little to no liver inflammation and normal serum aminotransferase levels. Serum HBeAg is detectable, and HBV DNA is markedly elevated.[10,11,15] As the host immune system matures, the patient enters the immune clearance phase, which is characterized by immune mediated liver injury. Patients who acquire infection as children come to clinical attention in this stage, and those who acquire infection as adolescents or adults have a very short or no immune tolerance phase and rapidly move into this second phase of the infection. Viral levels decrease, but HBV DNA is still elevated, and HBeAg is detectable. Serum aminotransferases increase, and liver histology shows active chronic hepatitis with evolving fibrosis.[10] Although most patients remain asymptomatic, some present with flares that mimic acute hepatitis, and this may precede the development of antibodies to HBeAg and remission of hepatitis activity.[10] Spontaneous seroconversion to HBeAb-positive status occurs in up to 90% of white adults with chronic hepatitis B within 10 years of follow-up, and it is more likely in those with high transaminase levels, which indicate a vigorous immune response to HBV.[10,15]

Seroconversion is followed by the low or nonreplicative HBsAg carrier stage, characterized by normalization of aminotransferases and low or undetectable HBV DNA levels.[10,15] Histologically, minimal to mild hepatitis with variable fibrosis is seen.[10] Most patients remain in this stage, particularly if they acquired the infection as adults; viral clearance may occur, but in patients with established cirrhosis, monitoring for HCC must continue.[10,16] Up to 20% of patients serorevert to HBeAg-positive status, with a flare of activity.[10,16] In up to one third of patients, chronic hepatitis recurs without seroreversion; this is known as HBeAg-negative chronic hepatitis, due to mutations in the precore or core-promoter regions of the HBV genome.[10,16] In this phase, despite the presence of anti-HBeAg antibody (HBeAb) and the absence of HBeAg, HBV DNA is detectable, serum aminotransferases rise, and histologic examination of the liver shows chronic hepatitis.[10] Patients with HBeAg-negative chronic hepatitis tend to be older and to have more advanced liver fibrosis.[10]

Cirrhosis develops at an annual incidence of 8% to 10% in patients with HBeAg-negative chronic hepatitis and 2% to 5% in patients with HBeAg-positive chronic hepatitis.[10] Cirrhosis is the major risk factor for the development of HCC; the annual incidence of HCC is 1% for HBV carriers without cirrhosis and 2% to 3% for those with cirrhosis.[10] The risk factors for cirrhosis and HCC are similar and include high HBV DNA levels, HBeAg positivity, older age, and male gender.[10,15] Additional risk factors for HCC include abnormal alanine aminotransferase levels, long duration of infection, coinfection with HCV or hepatitis D (HDV), a family history of HCC, excessive alcohol intake, cigarette smoking, HBV genotype C, and core-promoter mutations.[10]

Histopathology

Acute HBV infection is indistinguishable from other forms of acute viral hepatitis. Portal tracts exhibit a moderate to marked lymphocytic infiltrate. Lobular mononuclear inflammation is associated with widespread lobular injury in the form of hepatocyte ballooning, although in the early stages the injury may be confined to centrilobular regions. Numerous acidophil bodies, canalicular cholestasis, and Kupffer cell hyperplasia may be seen. In more severe cases, bridging necrosis may span between portal tracts and central veins. Panacinar necrosis or multiacinar necrosis may also be a feature. Fulminant cases are characterized by submassive or massive necrosis with marked ductular reaction. Numerous macrophages laden with lipofuscin and hemosiderin may be seen in necrotic areas. Hepatic lobular regeneration may also be evident, with mitotic figures and lobular disarray. The latter can be highlighted by reticulin stains, which serve to delineate the loss of normal hepatic plate architecture.

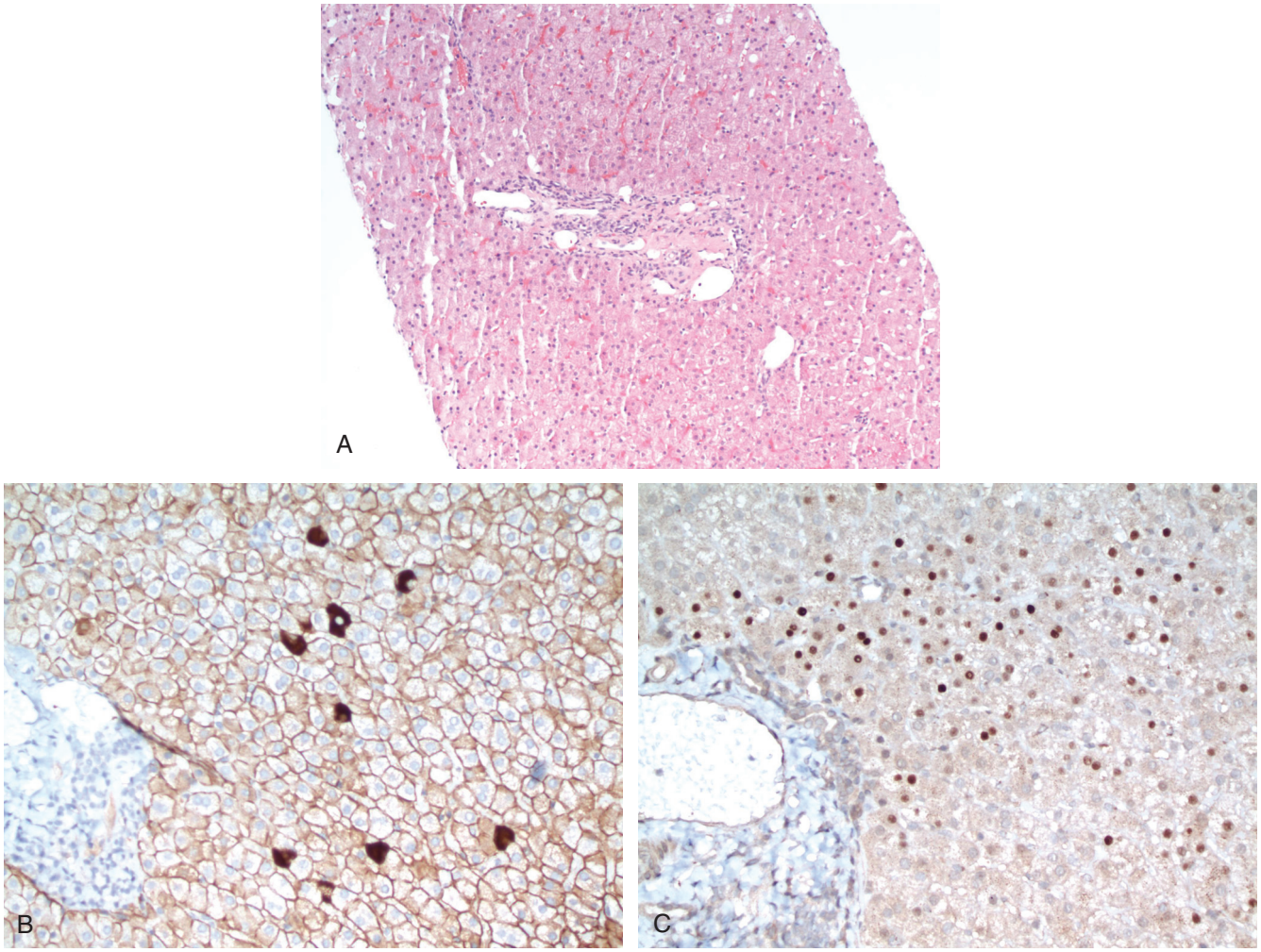

Figure 10-2. Liver biopsy in the immune tolerance phase of hepatitis B. **A,** Portal tract without inflammation or fibrosis. **B,** Immunohistochemical staining for hepatitis B surface antigen (HBsAg) shows strong membranous staining of hepatocytes as well as individual hepatocytes with strong cytoplasmic staining, consistent with high viremia. **C,** Immunohistochemical stain for the core antigen (HBcAg) shows nuclear staining of many hepatocytes, consistent with high viral replication.

The histology of chronic hepatitis B varies according to the phase of the disease and host immunity. The immune tolerance phase may show no or minimal portal and lobular inflammation and no fibrosis, despite rapid viral replication (Fig. 10-2). In the immune clearance phase, chronic hepatitis B shows portal mononuclear infiltrates with interface hepatitis and variable fibrosis (Fig. 10-3). Varying degrees of lobular necroinflammatory activity are present, but typically not to the extent seen in acute viral hepatitis. Hepatocyte anisonucleosis may be conspicuous. A characteristic feature of chronic HBV is the presence of ground glass hepatocytes (Fig. 10-4), which contain HBsAg. These hepatocytes show a finely granular cytoplasmic inclusion that displaces the nucleus and is surrounded by a pale halo. Ground glass hepatocytes can be demonstrated by various histochemical stains such as Victoria blue, orcein, or aldehyde fuchsin[17] and by immunohistochemical stains for HBsAg. In some cases, the hepatocyte nuclei have a "sanded" appearance due to the accumulation of HBcAg, although these are difficult to recognize and also are seen in delta hepatitis.[17]

Immunohistochemistry

Immunohistochemistry for HBV antigens can be used to evaluate the pattern of antigen expression, which correlates with viral replication and disease activity (Table 10-1). Strong cytoplasmic expression of HBsAg in scattered individual hepatocytes, associated with membranous staining of many hepatocytes, indicates high viremia and is seen in the immune tolerance phase.[18,19] In contrast, cytoplasmic expression of HBsAg in clusters of hepatocytes is more often seen in patients with low or absent viremia and without active viral replication; these cells contain integrated HBV DNA, and clonal expansion of such cells may explain their clustering.[18,19]

Expression of HBcAg can be cytoplasmic or nuclear. Nuclear expression correlates with the degree of viral replication; therefore, biopsy specimens from patients in the immune tolerance phase or from immunosuppressed patients often show widespread nuclear staining, whereas those from patients with chronic hepatitis and low-replicative states have rare positive nuclei. Cytoplasmic HBcAg expression is associated with active liver

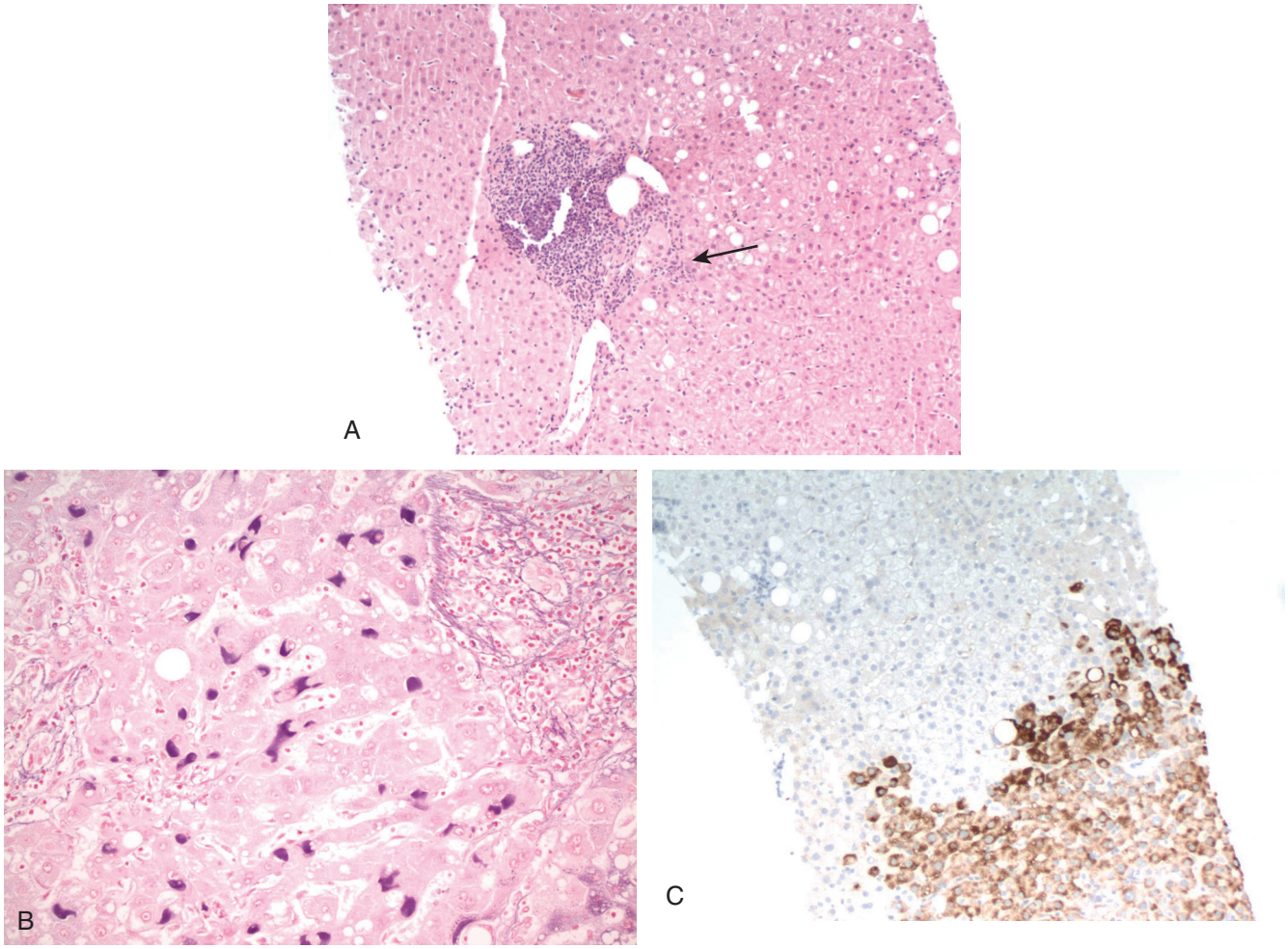

Figure 10-3. Liver biopsy in the immune clearance phase of hepatitis B. **A,** Low-power view of a portal tract with a dense mononuclear infiltrate and focal interface hepatitis *(arrow)*. **B,** Aldehyde fuchsin stain confirms the accumulation of hepatitis B surface antigen (HBsAg) within hepatocytes. **C,** Immunohistochemical stain for HBsAg shows cytoplasmic staining of clusters of hepatocytes, indicative of low viremia.

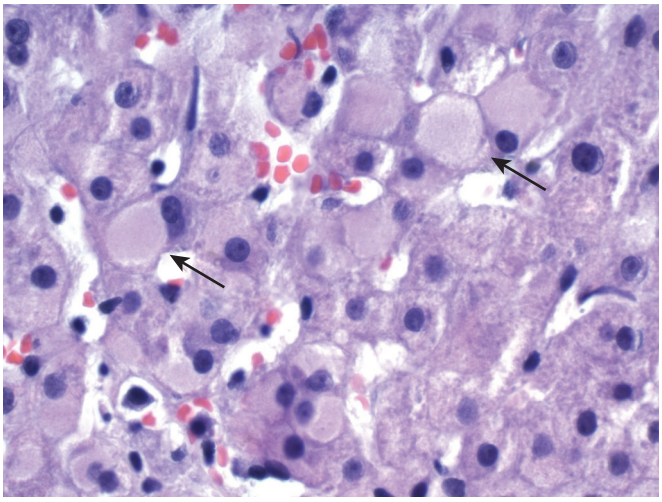

Figure 10-4. Ground glass hepatocytes in chronic hepatitis B *(arrows)*. Ground glass hepatocytes show finely granular cytoplasmic inclusions that displace the nucleus to the edge of the cell and are surrounded by a clear halo.

damage and suggests that HBcAg is the likely target for immune-mediated cytolysis.[18] Coinfection with delta virus can suppress HBcAg production and is one possible cause of a negative HBcAg stain in the setting of active hepatitis.

In general, immunohistochemistry findings for HBV antigens are negative in acute or fulminant hepatitis. Presumably, the inability to detect HBV antigen expression is a result of the short time interval of infection and insufficient accumulation of the proteins in hepatocytes to permit detection by immunohistochemistry.

Management

The management of chronic HBV infection has improved significantly in the last decade with the introduction of nucleoside and nucleotide analogues. These agents are orally administered, safe, well tolerated, and very effective at suppressing HBV DNA replication. However, sustained virologic suppression is not maintained after withdrawal of the agents, and long-term, indefinite therapy is often required. Long-term use of these agents is

Table 10-1 Immunohistochemistry for Hepatitis B

	HBsAg		HBcAg	
	Membranous	**Cytoplasmic**	**Nuclear**	**Cytoplasmic**
Immune tolerance phase	++	++ (individual cells)	++	
Immune clearance phase	–/+	+ (individual cells)	+ (few cells)	+/–
Low-replication states (chronic carriers)	–	++ (clustered cells)	–/+ (rare cells)	–
HDV/HCV coinfection	+	+/–	–	
HBV in immune-deficiency states	++	+/–	++	+

–, absent; +, present; HBcAg, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus.

also associated with the development of resistance, loss of clinical response, hepatitis flares, and even death.

Viral Mutants

Precore and Core Gene Mutations

Precore and core gene mutations are associated with decreased production of HBeAg despite continued production of infectious virions. The most common mutation results in a stop codon that prematurely terminates the synthesis of HBeAg.[15] Other mutations in the basic core promoter downregulate HBeAg synthesis at the transcriptional level.[15] Patients infected with these mutants exhibit absent HBeAg but positive HBsAg, elevated serum HBV DNA, and elevated transaminases.

Surface Gene Mutations

Surface gene mutations are responsible for vaccine escape. Although patients infected with these mutants are infectious, HBsAg is not detectable.[12]

Polymerase Gene Mutations

Mutations in the YMDD catalytic site of the polymerase significantly reduce the effectiveness of lamivudine and famciclovir.[12,20] Despite developing this mutation, patients continue to receive some benefit from lamivudine therapy, because the YMDD variant HBV exhibits reduced replication competence and reduced virulence.[12] Discontinuation of lamivudine may cause mutant virus to revert to wild-type, with renewed efficacy of lamivudine.[20]

Post-transplantation Hepatitis B

HBV frequently infects liver allografts after transplantation for HBV and may lead to deterioration of graft function, although some patients enjoy excellent graft function for many years despite active viral replication.[21] The risk of reinfection is greater after transplantation for chronic HBV infection with cirrhosis, compared to acute HBV.[22] The pattern of hepatitis in this setting ranges from purely immunohistochemical evidence of viral antigen expression without histologic features of HBV infection, to acute hepatitis, and to chronic hepatitis with cirrhosis.[21] Acute HBV hepatitis after transplantation may show marked ballooning and degenerative changes in the hepatocytes, scattered acidophil bodies, and extensive immunohistochemical evidence of viral antigen expression, but with remarkably scant inflammation.[21,22]

A distinctive pattern of hepatitis in the transplantation population is known as fibrosing cholestatic hepatitis, initially described by Davies and colleagues in 1991.[21-24] This pattern is characterized by canalicular and cellular cholestasis, ballooning of hepatocytes, and scattered acidophil bodies with relatively scant parenchymal inflammation. Portal tracts are mildly to moderately inflamed and show periportal fibrosis, with immature fibrous tissue extending as thin perisinusoidal strands into the acinus. At the interface, a proliferation of ductal-type cells lends a hypercellularity to the portal areas. Immunohistochemical stains show extensive cytoplasmic and membranous expression with HBsAg and extensive nuclear and cytoplasmic HBcAg.[21,23,24] The combination of high HBV antigen expression, marked hepatocyte injury, and relatively little inflammation suggests that the virus itself may be cytopathic in this setting.[21,22,24] Fibrosing cholestatic hepatitis is associated with a high rate of viral replication, with high serum HBV DNA, high serum HBsAg titers, and rapid deterioration.[22-24] It has also been described in HBV infection in other settings involving immunosuppression, including human immunodeficiency virus (HIV) infection[25] and bone marrow transplantation.[26]

Coinfection with Hepatitis B Virus and Human Immunodeficiency Virus

Approximately 90% of HIV-infected persons show evidence of prior HBV infection, and 5% to 15% have chronic HBV infection.[27] In patients coinfected with HIV and HBV, the rate of clearance of HBsAg and HBeAg is reduced, compared with non–HIV-infected individuals.[28] This reduced clearance rate is most likely due to a weakened immune system. However, the reduced immune reaction is potentially responsible for the relatively reduced inflammation in these patients despite their higher HBV viral replication rates.[28] Even though there is reduced inflammation, HBV infection is more progressive in HIV-positive patients, including development of cirrhosis and its complications.[28] A pattern of hepatitis similar to fibrosing cholestatic hepatitis has been described in HIV patients with concurrent HBV infection.[25] The HBV-related mortality in HIV patients has increased since the introduction of highly active antiretroviral therapy (HAART), possibly because of increased immunologic injury to the liver with immune reconstitution, toxicity of the antiviral

drugs, or longer life spans in HIV patients.[28] Conversely, the use of antiretroviral agents that also have activity against HBV may slow the progression of chronic HBV and even result in seroconversion, whereas their discontinuation can cause significant liver disease due to re-emergence of HBV replication.[27]

Hepatitis C

Hepatitis C affects between 123 and 170 million people worldwide.[29]

Virology

HCV is an RNA flavivirus that was characterized in the late 1980s.[29] Its genome is a positive, single-stranded RNA with a large open reading frame that encodes a 3010- to 3030-amino-acid polyprotein.[30] This polyprotein is processed into an array of structural and nonstructural proteins. The structural proteins include the core protein and two envelope proteins, E1 and E2.[30] The nonstructural proteins are NS2, -3, -4A, -4B, -5A, and -5B (RNA polymerase).[30]

There are 6 major genotypes and more than 50 subtypes. However, the genome of HCV is highly mutagenic, and a given host carries a mixture of viral particles with closely related sequences known as quasispecies.[30,31] The high mutation rate may allow the virus to escape the immune system; patients with chronic infection harbor highly diverse quasispecies, whereas those who clear the infection have low virus diversity and patients with fulminant hepatitis have the lowest level of viral diversity.[31] Genotypes 1, 2, and 3 have worldwide distribution, but their relative prevalence varies geographically.[32] Genotype 1a is the predominant genotype in North America (70%).[33] In Japan, subtype 1b is responsible for up to 73% of infections. Subtypes 2a and 2b are common in North America, Europe, and Japan, whereas subtype 2c is common in northern Italy. Genotype 3 is endemic in Southeast Asia, and it is also prevalent among intravenous drug users in Europe and the United States.[33] Genotype 4 is prevalent in North Africa and the Middle East; genotype 5 is largely confined to South Africa; and genotype 6 is found in Hong Kong, Macao, and Vietnam.[32,33]

The genotype affects the rate of evolution to chronic hepatitis, the severity of liver disease, and the response to interferon (IFN) therapy.[32] For example, genotype 1 is associated with a poor response to IFN therapy, whereas genotypes 2 and 3 respond more favorably.[33] An association between genotype 1b and an increased risk of developing severe liver disease and HCC has been reported.[33,34]

Natural History

HCV is primarily transmitted parenterally, such as by recreational drug use, injection with contaminated syringes or needles, or blood transfusion.[29,35] Although sexual and vertical transmission occur, they are less important with HCV than with HBV. The incidence of HCV in the United States has fallen since the introduction of widespread blood donor screening and needle-exchange programs.[31]

Acute infection can be diagnosed in a variety of ways, including documentation of anti-HCV seroconversion and detection of HCV RNA in the absence of HCV antibodies.[36-38] The mean incubation time for HCV is 6 to 8 weeks.[29] Although the majority (60% to 75%) of affected patients do not experience symptoms when acutely infected,[29] acute HCV still accounts for approximately 20% of cases of acute hepatitis.[35,39] The symptoms of acute HCV are malaise, fatigue, lethargy, anorexia, abdominal pain, jaundice, mild hepatosplenomegaly, maculopapular rash, and arthralgia.[29] Fulminant hepatitis is rare.

A minority of patients (approximately 15% to 50%) clear the infection, but most develop chronic viral hepatitis. Symptomatic onset of disease and female gender are associated with a higher chance of viral clearance after acute infection.[39] The serologic diagnosis of chronic HCV infection is made by detection of HCV antibodies, usually by enzyme immunoassay.[29] These assays have a 95% to 99% sensitivity and can detect antibodies 6 to 8 weeks after exposure. Polymerase chain reaction (PCR)–based methods can detect HCV RNA 1 to 3 weeks after exposure.[29] Patients with chronic HCV infection may present with normal transaminases. These patients are often identified during blood donation or screening. The rate of progression to fibrosis or cirrhosis is very low in this group.[35] Patients with elevated transaminases may suffer from fatigue or from nonspecific symptoms.[35]

Extrahepatic manifestations may include mixed essential cryoglobulinemia, membranous or membranoproliferative glomerulonephritis, non-Hodgkin lymphoma, Sjögren syndrome, lichen planus, autoimmune thyroid disease, and porphyria cutanea tarda.[29,35,40] A subset of patients with HCV demonstrate autoantibodies similar to those seen in autoimmune hepatitis, namely antinuclear antibodies (ANA), smooth muscle antibody (SMA), perinuclear antineutrophilic cytoplasmic antibody (p-ANCA), and anti-asialoglycoprotein receptor, although often at lower titer than is typically seen in autoimmune hepatitis.[40] Less often, liver-kidney microsomal (LKM1) autoantibodies are detected, although the epitopes recognized by these antibodies in HCV differ from those in autoimmune hepatitis type 2.[40] Patients with autoantibodies tend to be females and to have higher transaminase levels.[41] Some of these patients experience exacerbation during IFN-α therapy that may respond to steroid therapy, suggesting either preexisting autoimmune hepatitis or induction of autoimmune hepatitis in these patients.

The rate at which chronic hepatitis C progresses to cirrhosis depends on several factors. Factors that increase the rate of progression include male gender, older age at infection acquisition, longer duration of infection, immune suppression (e.g., HIV coinfection), HBV coinfection, alcohol use, and obesity.[29] The risk of developing cirrhosis is approximately 20% to 30% after 10 to 20 years of infection.[35] Once cirrhosis has developed, the risk of liver disease–related mortality is 2% to 5% per year and the risk of developing HCC is 3% to 5% each year.[35]

Histopathology

Acute hepatitis C is characterized by panlobular inflammation, numerous acidophil bodies, and lobular disarray similar to that seen in other acute hepatitides. A sinusoidal pattern of inflammation can mimic EBV hepatitis. More severe patterns of acute hepatitis, such as bridging necrosis or panacinar necrosis, are typically absent. Portal tracts harbor dense mononuclear infiltrates, resembling chronic HCV infection (Fig. 10-5). Bile duct injury may be present. Cholestatic forms of acute HCV

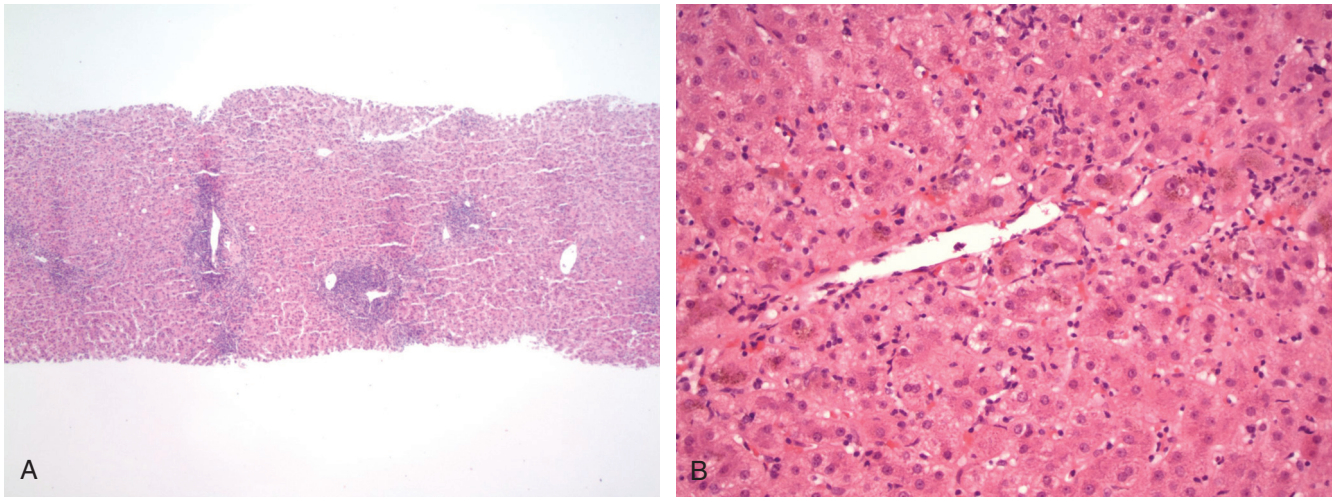

Figure 10-5. Liver biopsy in acute hepatitis C. **A,** Low-power view shows mononuclear cell infiltrates within portal tracts, similar in appearance to chronic hepatitis C virus infection. **B,** High-power view of the centrilobular region shows sinusoidal lymphocytic infiltrates surrounding a central vein.

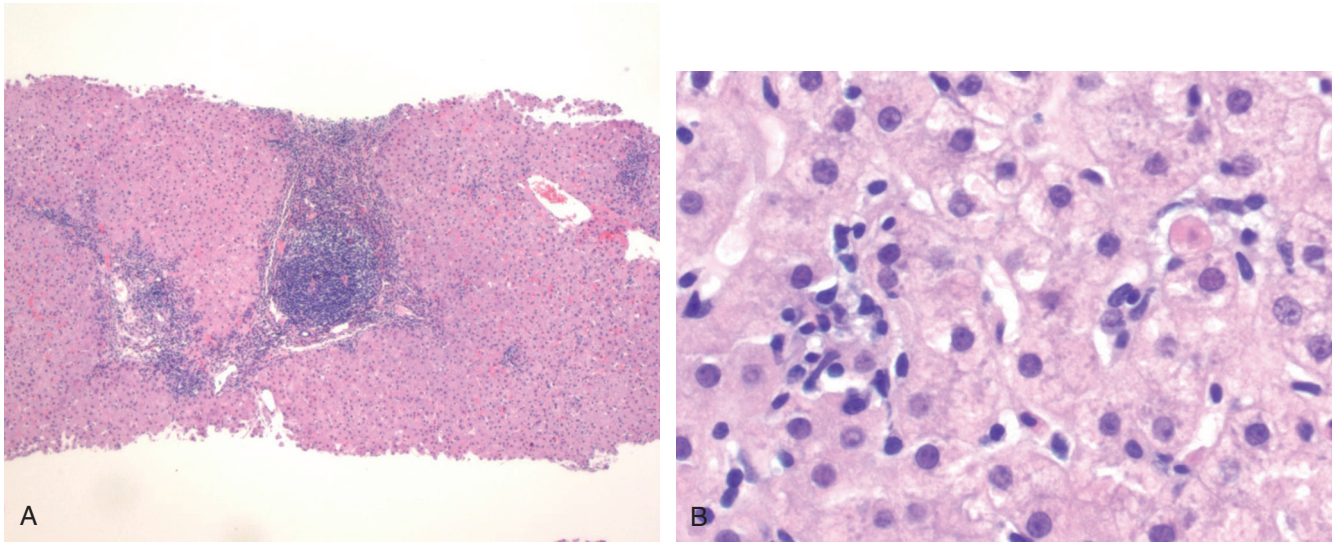

Figure 10-6. Liver biopsy in chronic hepatitis C. **A,** Low-power view shows a dense lymphoid aggregate within a portal tract. Bridging fibrosis is also evident, with mononuclear infiltrates in the septum. **B,** Lobular inflammation shows lytic necrosis on the left with a cluster of mononuclear cells indicating a focus of hepatocyte necrosis and a Councilman body (apoptotic hepatocyte) on the right; the latter is characteristic of hepatitis C virus infection.

infection occur rarely, predominantly in the immunosuppressed population.

Chronic HCV infection is characterized by dense mononuclear cell aggregates or follicles in portal tracts, with mild to moderate interface hepatitis.[42] Bile duct injury may be prominent, although typically it is mild. The lobules show scattered acidophil bodies (Councilman bodies) or foci of lytic necrosis marked by a small cluster of mononuclear cells (Fig. 10-6).[42] Kupffer cell prominence and lymphocytic infiltration of sinusoids may be seen.[17,42] Variable fibrosis is present, and its extent often drives the decision of whether to treat the infection.

Mild to moderate steatosis is characteristic of chronic HCV infection.[42] Steatosis may be related to direct viral cytopathic effects in patients with genotype 3 but to underlying metabolic status in patients with other genotypes.[43,44] HCV core protein expression produces steatosis in mice through mitochondrial toxicity and production of reactive oxygen species.[43] The severity of steatosis correlates with fibrosis.

Sarcoid-like granulomas are occasionally seen in liver biopsy specimens from patients with HCV. In one series, 9.5% of hepatic granulomas were attributed to HCV.[45] In another series, 5 (10%) of 52 liver explants for HCV-related cirrhosis had granulomas for which no other cause could be identified.[46] In a biopsy series, 14 of 155 biopsies for HCV had granulomas, but half of them could be ascribed to another cause (sarcoidosis, schistosomiasis, primary biliary cirrhosis, or mycobacterial infection).[47] In a large series of 542 biopsies for HCV, only 2% had granulomas. In that series, the presence of granulomas predicted a better response to IFN-α therapy.[48] Others have described granulomas in HCV after treatment with IFN-α in patients who did not respond well

to IFN-α.[49-51] In short, when a granulomatous process is encountered in a patient with HCV, other causes of granulomas in the liver must be rigorously excluded before they can be attributed to HCV. A history of IFN-α therapy should be sought.

The granulomas in HCV may occur in portal tracts or in the lobules. It is well known that HCV can be associated with mild bile duct injury. If the granulomas are in the portal area, their presence in conjunction with injured bile ducts may mimic primary biliary cirrhosis. Other clinical information (e.g., AMA, alkaline phosphatase level) may be needed to distinguish the two.

Management

Acute HCV infection is typically observed for 3 months after the onset of symptoms; antiviral therapy is offered to patients who have persistent viremia after that period.[36-38] The management of chronic HCV depends to some extent on viral genotype. Genotype 1 is associated with reduced likelihood of treatment success compared to genotypes 2 and 3. The mainstay of treatment is combination IFN and ribavirin. Treatment success has been improved with the introduction of pegylated IFN, which consists of a polyethylene glycol (PEG) polymer attached to the IFN molecule, which results in reduced drug clearance rates and allows once-weekly dosing.[29] Therapy may need to be continued for up to 24 weeks for genotypes 2 or 3 and up to 48 weeks for genotype 1.[29]

Post-transplantation Hepatitis C

After transplantation for chronic HCV, reinfection of the graft is almost universal. Although most patients do well in the long term, recurrent HCV can be progressive and can lead to graft dysfunction. The histologic features of recurrent HCV hepatitis progress from acute lobular hepatitis with scattered acidophil bodies and sinusoidal lymphocytic infiltration in the early stage to portal-based hepatitis with portal lymphoid aggregates typical of HCV infection in the chronic phase.[52] Progressive fibrosis and cirrhosis of the graft may result. A rapidly progressive cholestatic form of HCV infection has been described in the transplantation population, similar to the fibrosing cholestatic hepatitis described with HBV.[53] Fibrosing cholestatic hepatitis secondary to HCV has also been described in other immunosuppressed patient populations, such as in HIV patients[54] and after heart or kidney transplantation.[55-57]

Coinfection with Hepatitis C Virus and Human Immunodeficiency Virus

In the United States and Europe, 33% of HIV-infected persons are coinfected with HCV.[27] The clearance rate of HCV after acute infection is reduced in HIV-infected patients.[27] In chronic infection, HCV RNA levels are higher in HIV-coinfected patients, the efficacy of anti-HCV therapy is reduced, and the incidence of cirrhosis and HCC is higher.[20,27,28] In hemophiliac patients infected with HCV, coinfection with HIV has been associated with increased severity of hepatitis and increased risk of developing cirrhosis and liver failure.[58,59] Fibrosing cholestatic hepatitis related to HCV has been described in patients with HIV coinfection.[54] With the introduction of HAART, HCV-related liver disease has become an important factor in hospitalizations and mortality of HIV patients.[28] Patients with HCV are more likely to suffer from hepatotoxicity related to HAART and to have impaired immune reconstitution.[27]

Hepatitis D

HDV (delta virus) is a defective, single-stranded, circular RNA virus that requires the lipoprotein coat of HBV for its replication; therefore, infection from HDV alone does not occur. There are two modes of infection: coinfection with HBV and superinfection of prior HBV infection. Coinfection results in severe acute hepatitis with high mortality, but resolution produces immunity to both viruses. Superinfection is associated with a high likelihood of chronic infection by both viruses and a propensity for more severe inflammation than with HBV alone. HDV infection inhibits HBV replication, resulting in decreased expression of HBcAg, although expression of HBsAg continues.[7] Treatment with IFN-α inhibits HDV replication, but relapse is common.

HDV infection may be associated with autoimmune manifestations in a subset of patients. LKM3 autoantibodies are detected in 13% of patients with HDV.[40] However, one study found liver-specific autoantibodies (anti-asialoglycoprotein receptor) and non–organ-specific autoantibodies (e.g., ANA, anti-SMA) in 60.3% and 22.1% of HBV patients, respectively, regardless of whether HDV was present.[60] The pathology of HBV and delta virus is indistinguishable from that of HBV alone, except that the degree of inflammation and hepatocyte necrosis is often more prominent than with HBV alone.

Hepatitis E

Hepatitis E virus (HEV) is a nonenveloped, positive-sense, single-stranded RNA virus of the calicivirus family. Along with HAV, HEV accounts for the majority of cases of enterically transmitted viral hepatitis worldwide. However, unlike HAV, HEV is not easily transmitted from person to person, so familial clusters are unusual.[61] The virus is spread through fecally contaminated water or food, and epidemics have occurred in central and Southeast Asia, the Middle East, and North Africa.[61,62] Clinically, hepatitis E is indistinguishable from hepatitis A, and serology for anti-HEV IgM or PCR is required to make the diagnosis. Both are acute infections without progression to chronic hepatitis, and both can range from asymptomatic infection to fulminant hepatitis. The mortality rate is 1% to 4% overall, but it is approximately 20% among pregnant women.[61,62]

Although HEV is spread by the fecal-oral route, similar to HAV, there are some curious differences between the two viruses. In some countries where both viruses are endemic, such as India, children are universally infected with HAV by age 5 years, whereas HEV infects young adults and many adults are seronegative. In other countries, such as Egypt, seroconversion to anti-HEV occurs in a greater percentage of the population and at an earlier age. In the United States, anti-HEV is actually more common than anti-HAV, although HAV is more often diagnosed.[61] In developed countries, HEV infection is still only rarely diagnosed, although its incidence is increasing. Some evidence suggests that HEV may be a zoonotic infection: swine

have been shown to be frequently infected, and cases of zoonotic transmission to humans via ingestion of undercooked pork or deer meat have been reported.[61]

The histopathology of HEV is similar to HAV in that it can produce a classic acute hepatitis or cholestatic hepatitis with lobular canalicular cholestasis and relatively little inflammation. In some cases, cholangiolar proliferation with bile plugs in dilated cholangioles can be seen.

Epstein-Barr Virus

The liver is involved in more than 90% of cases of infectious mononucleosis, which is caused by Epstein-Barr virus (EBV) infection; hepatomegaly is present in 10% to 15% of cases, splenomegaly in 50%, and jaundice occurs in only 5%. Most often, the hepatic manifestations of EBV infection consist of self-limited elevations of hepatic transaminases. Rarely, EBV hepatitis has more serious consequences, such as the induction of autoimmune hepatitis,[63] severe hepatitis with prolonged jaundice,[64] or liver failure.[65-67]

Liver biopsy shows portal and periportal infiltrates of small and large lymphocytes, with occasional larger immunoblastic cells resembling the Reed-Sternberg cells of Hodgkin disease. A characteristic feature is sinusoidal infiltration by these same lymphocytes, which creates a beaded appearance (Fig. 10-7).[68] Liver cell ballooning is not prominent, although hepatocyte regeneration, canalicular cholestasis, and Kupffer cell hyperplasia are variably seen. Areas of necrosis may be infiltrated by collections of mononuclear cells, creating a granulomatous appearance. Although these histiocytes usually do not form true epithelioid granulomas, well-developed non-necrotizing granulomas[69] and fibrin ring granulomas have been reported in patients with EBV hepatitis.[70] In fatal cases, submassive lobular necrosis has been seen.[65]

Detection of EBV is done by in situ hybridization for EBV-encoded RNA (EBER) (Fig. 10-8) or by PCR for EBV DNA.[71] Immunohistochemistry for EBV latent membrane protein has not proved to be a reliable method for detecting EBV in EBV hepatitis.

Cytomegalovirus

Cytomegalovirus (CMV) infection is clinically mild and self-limited; CMV accounts for 8% of cases of infectious mononucleosis–like syndrome with hepatic involvement. Rare cases of massive hepatic necrosis have been reported, usually in immunocompromised hosts. In immunocompetent hosts, CMV infection can result in a histologic picture virtually identical to that of EBV hepatitis, with sinusoidal beading, atypical lymphocytes within sinusoids, lymphocytic infiltrates in portal tracts, and areas of necrosis with aggregates of Kupffer cells resulting in a granulomatous appearance.[72,73] CMV infection is rarely associated with well-formed non-necrotizing granulomas[74] or fibrin ring granulomas.[75] In immunocompromised patients, viral inclusions may be found in hepatocytes, endothelial cells, Kupffer cells, and duct epithelium (Fig. 10-9). Virally infected cells show a large amphophilic nuclear inclusion surrounded by a halo, known as an "owl's-eye" nuclear inclusion, and coarsely granular cytoplasmic inclusions. The inclusions may be isolated, or they may elicit an inflammatory reaction that can be granulomatous or neutrophilic, the latter being especially common in transplantation patients.[72] In HIV-positive patients, bile duct involvement may result in sclerosing cholangitis (HIV-associated cholangiopathy). Immunohistochemical stains for CMV can highlight cells with inclusions, including atypical inclusions.

Herpes Simplex Virus

Herpes simplex virus (HSV) viremia can result in visceral involvement, affecting mainly the esophagus, lungs, and liver. Liver involvement occurs primarily in neonates, pregnant patients, and immunocompromised patients, although immunocompetent adults are rarely affected as well.[76] HSV hepatitis is rapidly lethal

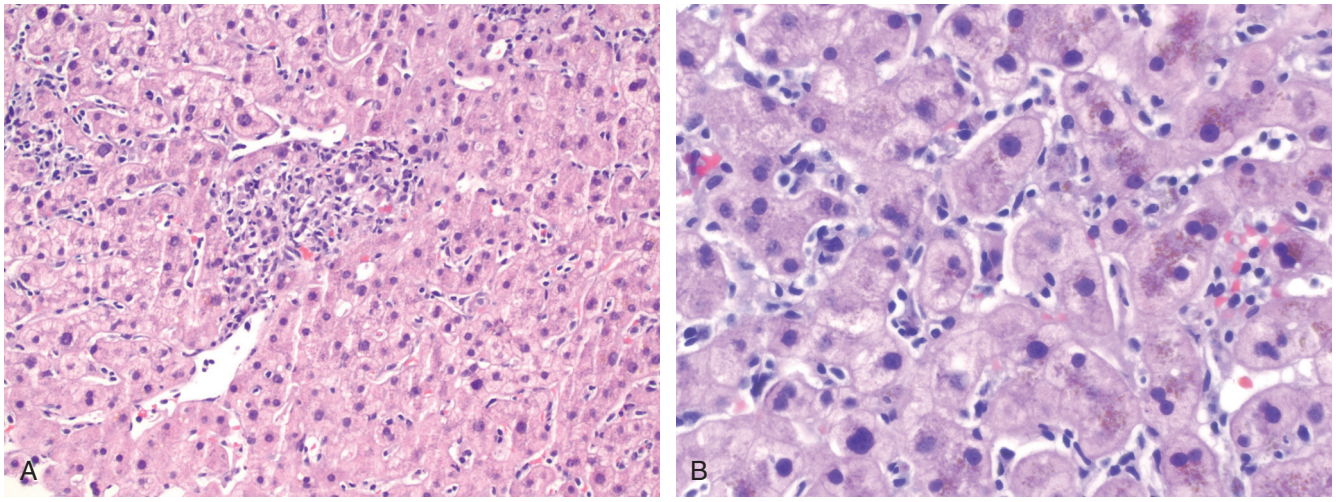

Figure 10-7. Liver biopsy in Epstein-Barr virus infection. **A,** A portal tract shows a mild mononuclear infiltrate, and the lobules show infiltration of sinusoids by mononuclear cells. **B,** High magnification shows prominent sinusoidal lymphocytic infiltration without hepatocyte necrosis.

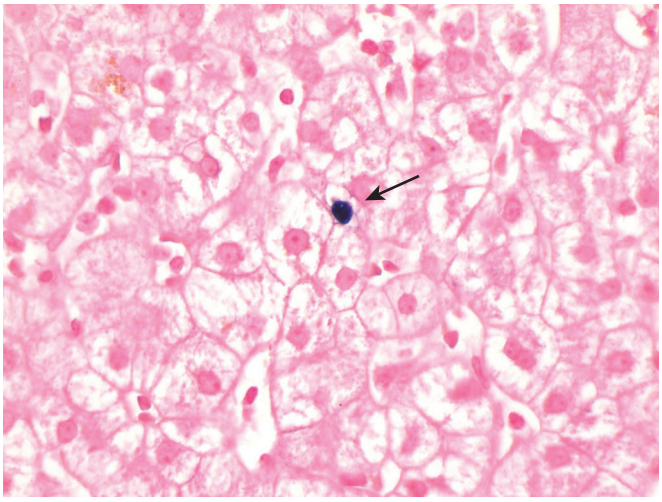

Figure 10-8. In situ hybridization for EBV-encoded RNA (EBER) shows nuclear staining of a single infected lymphocyte *(arrow)*.

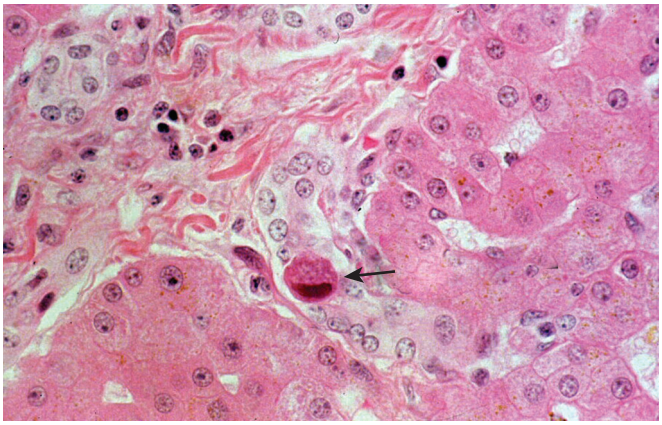

Figure 10-9. Cytomegalovirus (CMV) infection, demonstrating a CMV inclusion in bile duct epithelium *(arrow)*. (Courtesy of Dr. Laura Lamps.)

and requires early recognition and institution of antiviral therapy to improve outcome.

HSV hepatitis is characterized by patchy, nonzonal coagulative necrosis with minimal to absent inflammatory response (Fig. 10-10). Intranuclear inclusions of two types can be found in hepatocytes at the edge of the necrotic foci, and virally infected cells are often multinucleated.[76] Cowdry type A inclusions are large, eosinophilic intranuclear inclusions surrounded by a halo, whereas type B inclusions replace the entire nucleus with a basophilic ground glass appearance. Immunohistochemistry for herpes type I and type II antigens highlights the nuclear inclusions, and overlap between the two antibodies is frequent.[76]

Treatment with antiviral drugs before the biopsy is obtained may result in a biopsy specimen with extensive necrosis but without diagnostic inclusions.[76] The main differential is varicella-zoster virus (VZV) infection and adenovirus infection, both of which have a similar histologic appearance; immunohistochemical staining or PCR may be necessary to distinguish these infections. HSV serologic studies are not helpful in establishing the diagnosis.

Varicella-Zoster Virus

Rarely, the rash of VZV can be accompanied by potentially life-threatening noncutaneous manifestations, including encephalitis, pneumonitis, myocarditis, and hepatitis, especially in immunocompromised patients. In children, the convalescent phase can be associated with Reye's syndrome (microvesicular steatosis, hyperammonemia, coagulopathy, and cerebral edema), particularly if aspirin has been administered. Primary infection in immunocompetent adults can cause severe acute hepatitis and, rarely, fulminant hepatic failure. Transplantation patients and immunocompromised patients are at higher risk for a fatal fulminant hepatitis.

Serology is of little use, especially in the immunocompromised patient. The appearance on liver biopsy resembles HSV. Immunohistochemistry can confirm the presence of a herpes

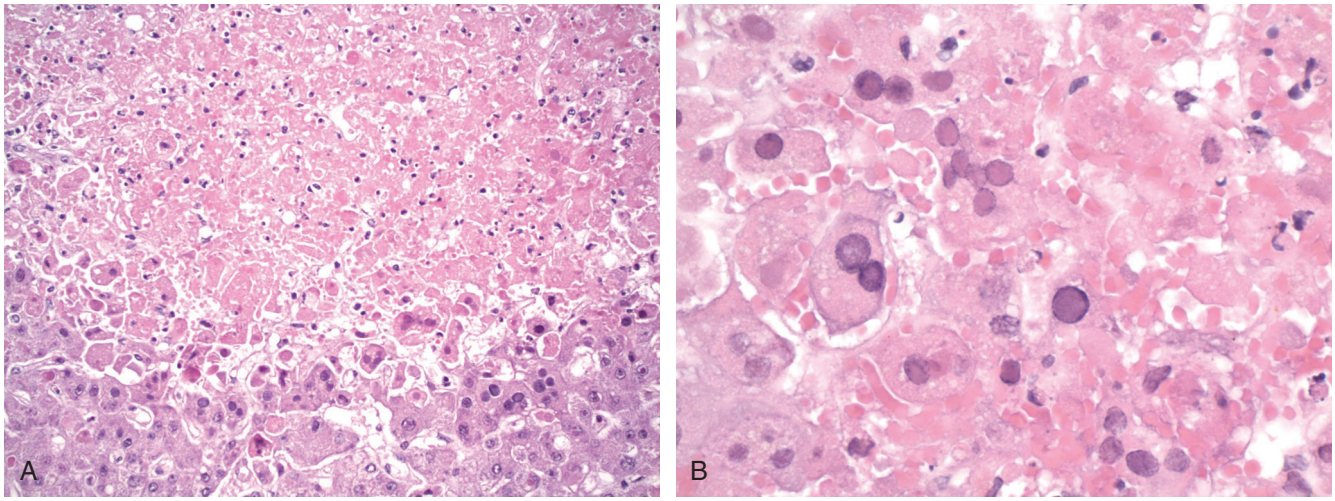

Figure 10-10. Herpes simplex virus (HSV) infection. **A,** The liver shows necrotic regions without an inflammatory response. **B,** Hepatocytes at the edge of the necrotic regions show glassy nuclear inclusions and multinucleation, consistent with HSV infection.

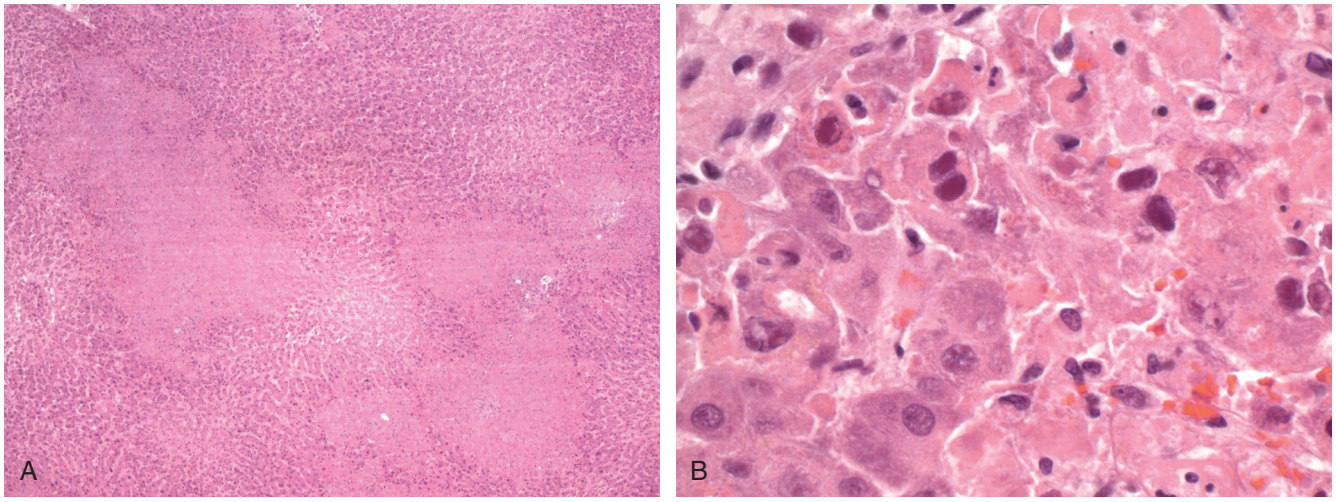

Figure 10-11. Adenovirus hepatitis. **A,** Low-power view shows several regions of necrosis without an inflammatory reaction. **B,** High-power view shows hepatocytes with smudgy nuclear inclusions similar to the Cowdry type A inclusions of herpes simplex virus.

virus, but, depending on the antibody, may not distinguish which one. PCR may be necessary to distinguish HSV from VZV infection.

Adenovirus

Although infection by adenoviruses is generally restricted to the upper respiratory tract and conjunctivae in the normal host, disseminated infection can occur in immunodeficient patients. Postmortem livers in patients with adenovirus hepatitis have shown widespread necrosis with little inflammation, mild steatosis, and viral inclusions similar to the Cowdry type A inclusions of HSV infection (Fig. 10-11).[77,78] Immunohistochemistry, electron microscopy, and viral culture are helpful in making the diagnosis.[78]

Parvovirus B19

Parvovirus B19 produces several clinical manifestations, including erythema infectiosum (fifth disease) in children; hydrops fetalis; arthritis associated with acute infection in adults; various hematologic disorders (e.g., leukopenia, thrombocytopenia, transient aplastic crisis); and, rarely, involvement of other organs, including neurologic, cardiac, hepatic, and vascular disease.

The role of parvovirus B19 infection in acute or fulminant hepatitis is controversial. Parvovirus B19 DNA has been found in the liver of patients with fulminant hepatic failure and in the serum of patients with acute or fulminant hepatitis, suggesting a role for this virus in cases of unexplained acute hepatitis or acute liver failure.[79-81] In one study,[80] parvovirus B19 DNA was found in liver tissue in four of six patients with fulminant hepatic failure associated with aplastic anemia and in two of four patients with cryptogenic acute liver failure (without aplastic anemia), but not in six patients with known causes of acute liver failure. Histology studies in DNA-positive cases showed massive hepatic necrosis and collapse without inflammatory infiltrates or viral inclusions. In contrast, other investigators found no parvovirus B19 DNA by PCR in 33 cases of cryptogenic acute liver failure but detected parvovirus B19 DNA in several patients with known causes of acute liver failure.[82] In that study, several patients had low-titer IgM positivity without confirmatory PCR positivity. In another study, parvovirus B19 DNA was found with similar frequency in patients with fulminant hepatitis and with hepatitis B or C. Furthermore, RNA transcripts could not be detected in any of the liver tissue samples, arguing against active viral replication.[83] These studies suggest that low levels of PCR positivity may reflect remote infection, and they raise questions about the role of parvovirus B19 in hepatitis and acute liver failure.

Rubella (German Measles)

Acute hepatitis has been reported in adults who acquire rubella. The morphology shows ballooning degeneration of hepatocytes, focal hepatocyte necrosis, and infiltrating mononuclear cells, similar to classic acute hepatitis.[84,85]

Rubeola (Measles)

Measles is a contagious, acute, febrile illness that predominantly affects children and causes a maculopapular rash, Koplik spots, cough, conjunctivitis, fever, and lymphadenopathy. The virus enters the body through the lungs or conjunctivae, replicates at these sites, and then is transported to the reticuloendothelial system, where further replication and lymphoid proliferation occur. Transient transaminase elevation is not uncommon in measles.[86] In one reported case, liver biopsy demonstrated acute cholangitis, periportal inflammation with lymphocytes, eosinophils and neutrophils, periportal hepatocyte necrosis, ballooning degeneration and cholestasis, and multinucleated giant cells (Fig. 10-12). At autopsy, viral inclusions were noted in hepatocytes.[87]

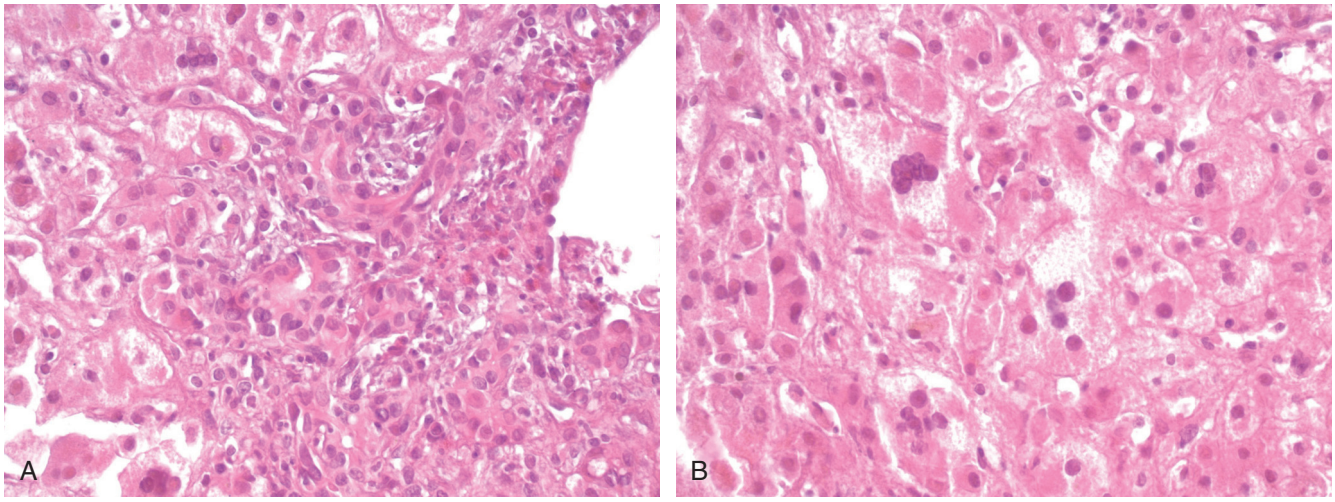

Figure 10-12. Liver biopsy in a patient with measles hepatitis. **A,** Portal tracts show inflammation, cholangitis with bile duct injury, periportal hepatocyte loss, and ballooning degeneration. **B,** The lobules show widespread hepatocyte ballooning degeneration, cholestasis, and multinucleated hepatocytes.

Severe Acute Respiratory Syndrome Coronavirus

In 2003, a novel coronavirus was found to be the causative agent of severe acute respiratory syndrome (SARS), an atypical pneumonia that can progress rapidly to acute respiratory distress syndrome. Hepatic impairment is common in these patients, with elevated transaminases seen in approximately 60% of cases. Liver histology shows lobular hepatitis with occasional acidophil bodies, prominent Kupffer cells, increased numbers of hepatocyte mitoses, focal mild ballooning degeneration, and mild portal tract inflammation.[88]

Human Immunodeficiency Virus

HIV is associated with liver disease in several ways. During seroconversion, a small proportion of patients may experience hepatitis with transaminase elevations, although the histology of this hepatitis has not been described.[89,90] Opportunistic infections such as CMV, *Histoplasma capsulatum*, *Mycobacterium avium-intracellulare* complex (MAC), and *Pneumocystis jiroveci* can infect the liver. HIV can also increase the risk of progression of nonopportunistic pathogens, such as *Mycobacterium tuberculosis,* HBV, or HCV (see earlier discussions). Patients with the acquired immunodeficiency syndrome (AIDS) may develop unusual reactions to certain pathogens, such as bacillary epithelioid angiomatosis secondary to *Bartonella henselae* or *Bartonella quintana* infection (discussed later).[91,92]

Granulomas are a common finding in liver biopsy of patients with HIV infection. The more common causes are *M. tuberculosis,* MAC, *Histoplasma, Candida,* CMV, and *Cryptococcus.*[93] In some of these patients, the granulomatous response is poorly developed and composed of loose aggregates of histiocytes, but silver or acid-fast stains show numerous organisms. Therefore, acid-fast and silver stains should be done routinely on biopsy specimens from patients with HIV/AIDS.

AIDS-related cholangiopathy is a syndrome that manifests with right upper quadrant abdominal pain, fever, and marked elevations of serum alkaline phosphatase. On cholangiography, the bile duct shows strictures and irregularities indistinguishable from those of primary sclerosing cholangitis. Several opportunistic pathogens have been implicated in this disorder, including *Cryptosporidium*, CMV, and microsporidia (*Enterocytozoon bieneusi)*.[94-99] In a significant minority of cases, there is no identifiable pathogen; it is unclear whether these cases are due to unknown pathogens, occult infection, altered immunity, direct infiltration of the bile duct mucosa by HIV, or primary sclerosing cholangitis coincidentally occurring in patients with AIDS.[98,99]

The liver can be involved by HIV-associated neoplasms such as lymphoma or Kaposi sarcoma.[100] The latter is caused by another virus, Kaposi sarcoma–associated herpesvirus (KSHV), also known as *Human herpesvirus 8* (HHV-8). Finally, immune reconstitution with HAART can precipitate autoimmune hepatitis.[101]

Yellow Fever

Yellow fever is a viral hemorrhagic fever that can vary from subclinical to rapidly fatal. It is transmitted by the *Aedes* mosquito. Classic symptoms include sudden onset of fever, rigors, and headache. Jaundice and hemorrhagic manifestations portend a poor prognosis. The pattern of injury is frequently described as midzonal and sometimes centrilobular.[102-105] Others describe panlobular injury with only a collar (one or two cells thick) of preserved hepatocytes around central veins and portal tracts.[106] The key findings are necrosis with numerous apoptotic hepatocytes (Councilman bodies), microvesicular steatosis, and absence of inflammation (Fig. 10-13).[102-106] Eosinophilic intranuclear inclusions, Torres bodies, are rarely seen in humans.[106] Immunoperoxidase assays are not widely available, but the diagnosis

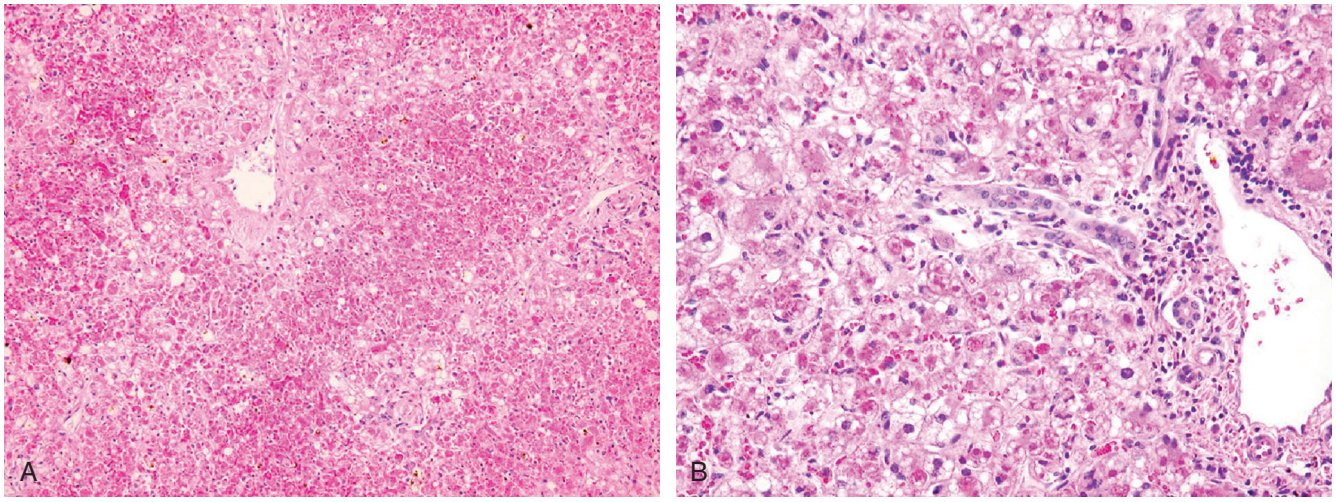

Figure 10-13. Yellow fever. **A,** Low-power view shows panlobular necrosis with numerous necrotic hepatocytes primarily in zones 2 and 3. **B,** High-power view shows relative preservation of periportal hepatocytes with steatosis, ballooning degeneration, and scattered necrotic hepatocytes. (Courtesy of Dr. Shu-Yuan Xiao.)

can be confirmed serologically. The differential diagnosis includes other viral hemorrhagic fevers such as dengue and Rift Valley fever.

Dengue

The dengue virus, a member of the Flaviviridae family, is also transmitted by the *Aedes* mosquito. Dengue virus infection is one of the most important mosquito-borne diseases in the world, and the resurgence of this disease in the last 2 decades may be related to human population growth, inadequate wastewater management, lack of effective mosquito eradication programs, and emergence of more virulent strains.[107] The clinical manifestations include dengue fever, dengue hemorrhagic fever, or dengue shock syndrome. Dengue fever manifests as high fever, severe headache, arthralgias, myalgias, and sometimes a rash. Patients with dengue hemorrhagic fever suffer from bleeding phenomena and circulatory failure. Dengue shock is caused by severe plasma leakage and manifests as cyanosis, hypotension, and encephalopathy.[107] There are four serotypes of dengue virus, and infection with one serotype confers future protective immunity against that serotype only. Infection with a second serotype may result in antibody-dependent enhancement of the illness with immune complex formation.[107]

The severity of hepatic involvement parallels the severity of the dengue infection. Serotypes 3 and 4 are associated with more severe liver disease.[107] The histology is characterized by necrosis, with Councilman bodies involving the centrilobular region or, as in yellow fever, zone 2, although in most cases the degree of necrosis is not as severe as in yellow fever (Fig. 10-14).[105,106] The contributions of virus or shock to the centrilobular necrosis remain uncertain.[106] Microvesicular steatosis is frequent, although relatively mild. As with other arboviruses, little inflammation is present.[108,109] The distinction from yellow fever may require geographic data, clinical features, and virologic studies. Immunohistochemical demonstration of the virus within hepatocytes has been described.[108,109]

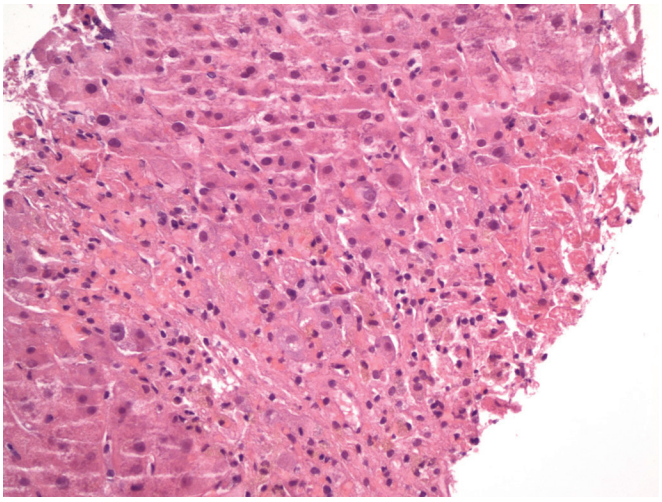

Figure 10-14. Liver biopsy specimen from a patient who died of dengue shock demonstrates centrilobular necrosis with numerous acidophil bodies *(right)* and no inflammatory reaction.

Rift Valley Fever

Rift Valley Fever primarily affects sheep and cattle in Africa, although humans who have direct contact with animals or carcasses may become infected. Fever, severe headache, and myalgia may be followed by facial inflammation, encephalitis, and macular degeneration.[102] Hemorrhage and jaundice are poor prognostic features. Autopsies of cases with hemorrhage show hepatic necrosis, either widespread or predominantly in the periportal and midzonal areas; numerous acidophil bodies; and hemorrhage.[102,106]

Lassa Virus

Lassa virus is associated with severe febrile illness among missionaries and travelers returning from West Africa. Symptoms

include chills, malaise, headache, and myalgia. Petechiae, ulcerative tonsillitis, and lymphadenopathy are common.[102] The liver shows haphazardly distributed areas of hepatocyte necrosis, both as foci of contiguous cells and as individual cells, either acidophilic or coagulative in type.[106,110] There is little inflammatory reaction apart from histiocytes phagocytosing necrotic debris.[110] The nonzonal distribution of the necrosis distinguishes this disease from yellow fever.[102,110]

Ebola Virus

Ebola virus causes a severe and frequently fatal viral hemorrhagic fever; outbreaks in Sudan and Zaire have caused international concern. The disease is similar to Marburg virus infection, with disseminated intravascular coagulopathy and bleeding occurring in the majority of patients.[102] The histology is characterized by foci of hepatocellular necrosis randomly distributed throughout the parenchyma and eosinophilic inclusions within hepatocytes.[102,106] Mild to moderate steatosis, mild mononuclear infiltrates in the periportal area, and Kupffer cell activation are additional findings.[106]

Marburg Virus

Marburg virus has been associated with African green monkeys. Fever, malaise, headache, and myalgia may be accompanied by a maculopapular rash and conjunctivitis.[102] The histology is similar to that of Ebola virus infection. On electron microscopy, many hepatocytes contain inclusions composed of uniformly packed filaments arranged in parallel arrays.[102]

Mycobacteria

Tuberculosis

Worldwide, *M. tuberculosis* is one of the most common causes of hepatic granulomas. The organisms may reach the liver hematogenously from the lungs, through the portal circulation in the setting of gastrointestinal tuberculosis, or via lymphatics.[111] Tuberculosis (TB) can affect the liver in several forms. Most often, the liver is affected in the setting of generalized miliary TB.[112] Less often, hepatitic TB manifests as a localized mass lesion that mimics a neoplasm, causes obstructive jaundice from extrinsic compression of the hepatic duct, or causes portal hypertension from compression of the portal vein.[111,113] Localized hepatic involvement can occur in primary infection, in which case there is no evidence of antecedent infection, or as reactivation TB.[114] Tuberculous cholangitis, in which the bacillus primarily infects the biliary tree, is extremely rare.[115]

The most common presentation of hepatic TB is abdominal pain, hepatomegaly, jaundice, fever, and chills. Alkaline phosphatase elevations and hyponatremia usually are prominent features.[114,116,117] In 65% to 78% of patients with hepatic TB, respiratory symptoms or chest radiographs suggest pulmonary TB as well.[111,114,116,117] Abdominal imaging shows liver calcifications in approximately half of patients.[111,112,118] Caseating granulomas are a hallmark of hepatic TB, particularly miliary TB in the setting of primary infection; in reactivation TB, noncaseating granulomas may be present instead (Fig. 10-15). The granulomas may reside in the lobules or in portal tracts. Acid-fast stains or cultures are positive in 0% to 59% of cases, but organisms are more likely to be found with caseating necrosis.[114-116] PCR for *M. tuberculosis* DNA has a 53% to 88% sensitivity and a 96% to 100% specificity for detecting hepatic TB.[111,119,120] Immunocompromised patients may present with a wasting syndrome in which multiple organs, including the liver, contain necrotic miliary nodules surrounded by histiocytes that do not aggregate into well-formed granulomas. Acid-fast stain shows numerous organisms in these lesions.[121]

Localized hepatic TB includes tuberculoma and tuberculous abscess. Radiologically, it mimics tumors except that calcification may be prominent and may assume a bull's-eye configuration.[113] Grossly, localized hepatic TB appears as cheesy or chalky white, irregular nodules. Histologically, tuberculomas are composed of confluent granulomas, contain few organisms, and are encountered in immune-competent patients, whereas tuberculous abscesses are centrally suppurative, contain numerous organisms, and are encountered mainly in immunodeficient patients.

Biliary involvement manifests as obstructive jaundice which might have as its cause compression of the bile duct by a hepatic tuberculoma, small duct involvement by granulomas, or isolated biliary tree involvement.[112] The latter may result in bile duct strictures that can be mistaken for cholangiocarcinoma or primary sclerosing cholangitis.[112,122]

Mycobacterium avium-intracellulare Complex

Of the atypical mycobacteria, *Mycobacterium avium* and *Mycobacterium intracellulare* are significant hepatic pathogens. MAC is commonly encountered in immunocompromised patients, particularly those with AIDS. These organisms cause disseminated infection that commonly affects lung, liver, spleen, lymph nodes, and bone marrow. Patients with hepatic involvement present with fever, elevated alkaline phosphatase, and hepatomegaly.[123] The histopathologic findings range from numerous well-formed, nonnecrotizing granulomas with rare acid-fast organisms on Ziehl-Neelsen stain to less well-formed granulomas with large numbers of acid-fast organisms spilling out of the loose granulomas into nearby Kupffer cells (Fig. 10-16).[121,124] Although the latter pattern differs from the usual case of hepatic TB, the degree of immune compromise, rather than the species of mycobacteria, may be the more important factor in determining the number of organisms and type of granulomas seen, because T-cell function is required for the formation of well-formed granulomas, and hepatic TB in patients with AIDS also may show large numbers of organisms and few well-formed granulomas.[121,123]

Leprosy

Infection by *Mycobacterium leprae* commonly involves the liver, although clinical manifestations are often mild or absent. Hepatic granulomas are found in 90% of patients with lepromatous leprosy but in fewer than 20% of patients with tuberculoid leprosy.[125] The appearance of the granulomas depends on the type of leprosy. In lepromatous leprosy, collections of foam cells within the lobules

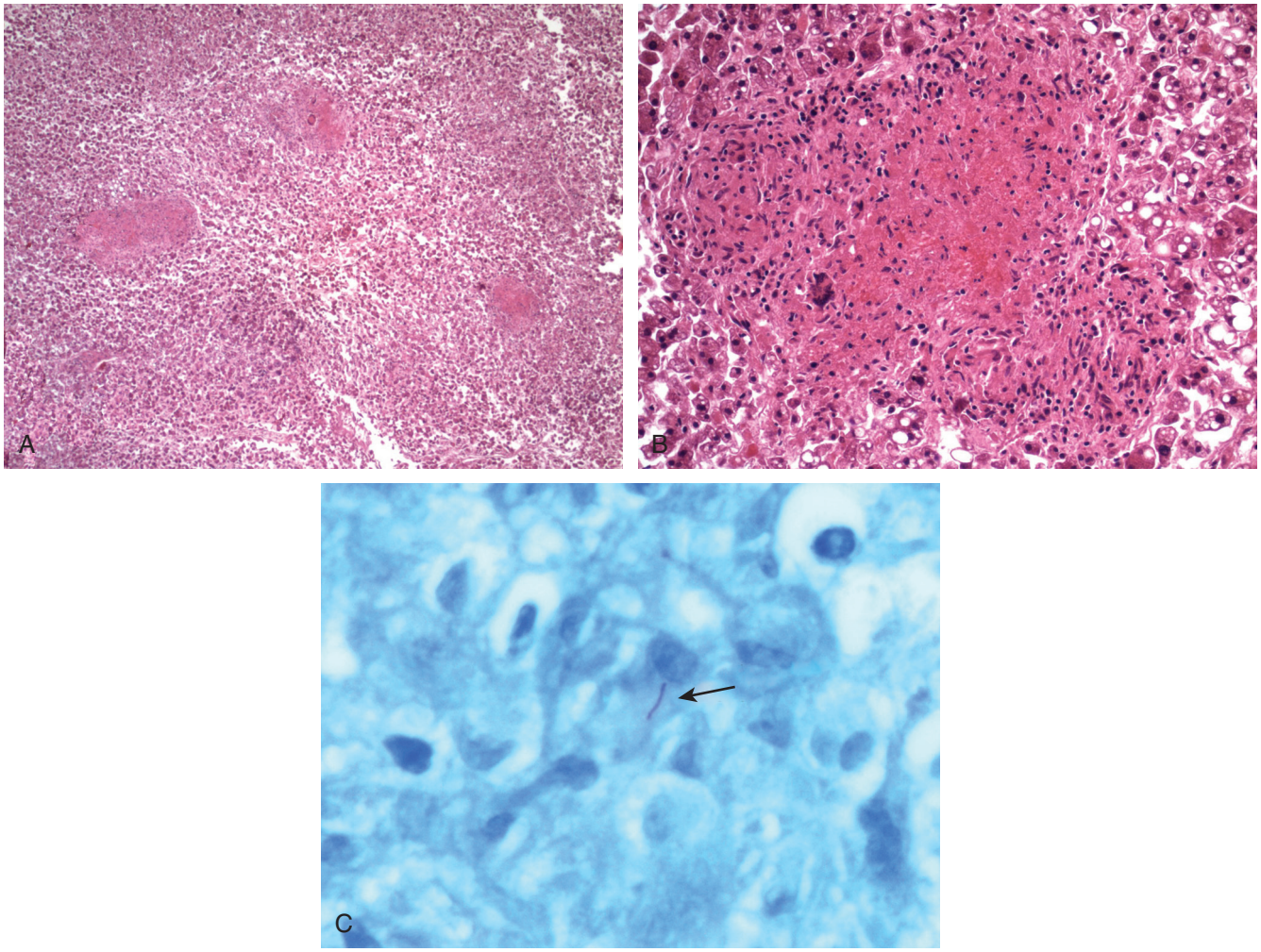

Figure 10-15. Miliary tuberculosis involving the liver. **A,** Low-power view shows several necrotizing granulomas. **B,** High-power view of a necrotizing granuloma. Note the central region of necrosis surrounded by histiocytes and a giant cell. **C,** An acid-fast stain highlights a single bacillus *(arrow)* within the granuloma.

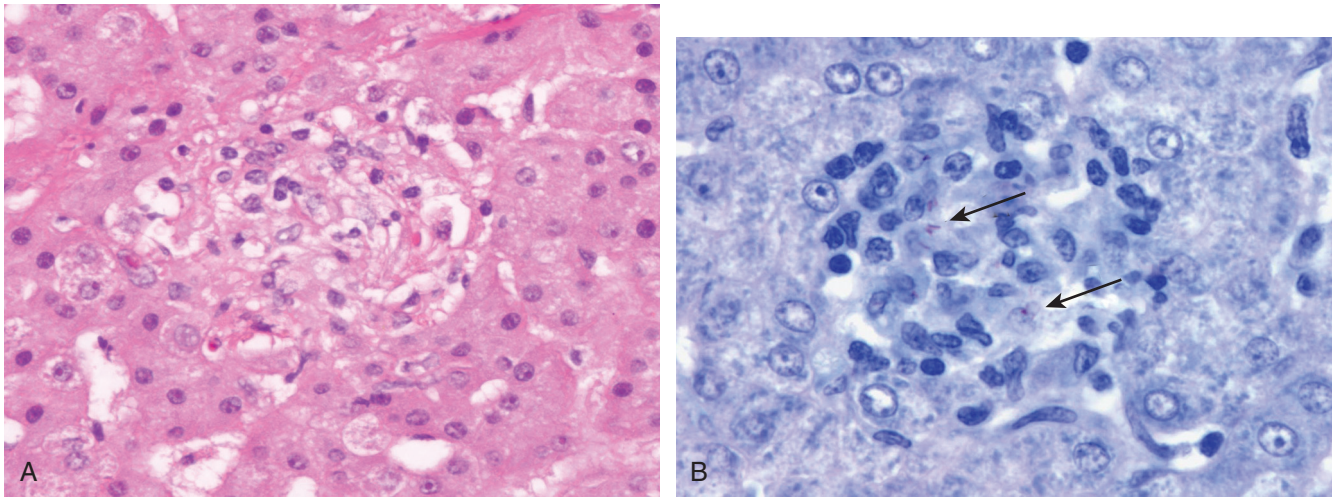

Figure 10-16. *Mycobacterium avium-intracellulare* complex (MAC) infection in an immunocompromised patient. **A,** The liver shows loose collections of histiocytes, suggestive of poorly formed granulomas. **B,** On acid-fast staining, several bacilli are present *(arrows)*.

or portal tracts contain numerous acid-fast bacilli.[125,126] In tuberculoid leprosy, epithelioid granulomas with rare or no acid-fast organisms are seen (Fig. 10-17).[125] An individual patient may have both lepromatous and tuberculoid granulomas.

Bacillus Calmette-Guérin

Bacillus Calmette-Guérin (BCG) is an attenuated form of *Mycobacterium bovis,* immunologically related to *M. tuberculosis,* that has been used as a vaccine against TB, as intralesional treatment of dermal malignancies, and as intravesical therapy for superficial bladder cancer. Hepatic granulomas have been described in patients after intradermal injections of BCG.[127,128] Pneumonitis or granulomatous hepatitis, or both, affect 0.7% of patients who receive multiple intravesical instillations of BCG and are more likely after traumatic catheterization, extensive tumor resection, or bladder perforation.[129] The liver shows noncaseating epithelioid granulomas, mild steatosis, and hepatocyte necrosis. Often, acid-fast bacilli are not identified, and cultures are negative. This has led to the suggestion that the granulomatous hepatitis represents a hypersensitivity reaction to antigens present in the BCG preparation,[127] particularly because some cases show additional features of extrahepatic granulomas, leukocytoclastic vasculitis, or bile duct injury and eosinophils (Fig. 10-18).[130,131] However, in some reported cases, acid-fast bacilli have been identified in the granulomas, blood cultures have been positive for *M. bovis,* or PCR for mycobacterial DNA has been positive, indicating disseminated BCG infection.[131-133] Some have suggested that two types of adverse reactions may occur, one a disseminated infection that responds to anti-TB therapy and the other a sterile hypersensitivity reaction that is delayed in appearance and responds to steroids.[131]

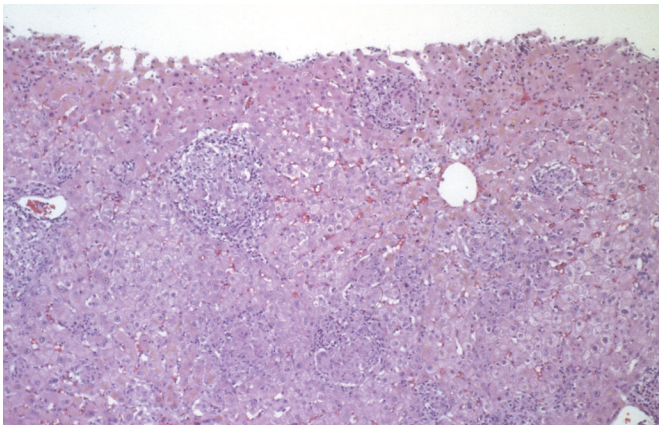

Figure 10-17. Liver biopsy sample from a patient with leprosy. Several noncaseating granulomas are present.

Nonmycobacterial Bacteria

Bacterial infections of the liver can produce a wide range of pathology, including hepatitis, parenchymal necrosis, microabscesses, pyogenic liver abscess, and granulomatous hepatitis. Mixed patterns are frequent, and many organisms can produce several patterns. Microabscesses or pyogenic liver abscesses can be caused by a multitude of aerobic and anaerobic organisms, fungi, and parasites. Granulomatous hepatitis with or without a necrotizing component can be seen in a number of infections (Table 10-2).[134-136] However, in some entities, the granulomas are not true epithelioid granulomas, but rather aggregates of histiocytes in foci of parenchymal necrosis. Because these "microgranulomas" do not generate the same differential diagnosis as true epithelioid granulomas, the diagnosis of "granulomatous hepatitis" in these cases is best avoided. Biliary involvement can produce acute cholangitis or cholecystitis.

Pyogenic Liver Abscess

Historically, pyogenic liver abscess was associated with acute appendicitis or intra-abdominal infection, and in those settings

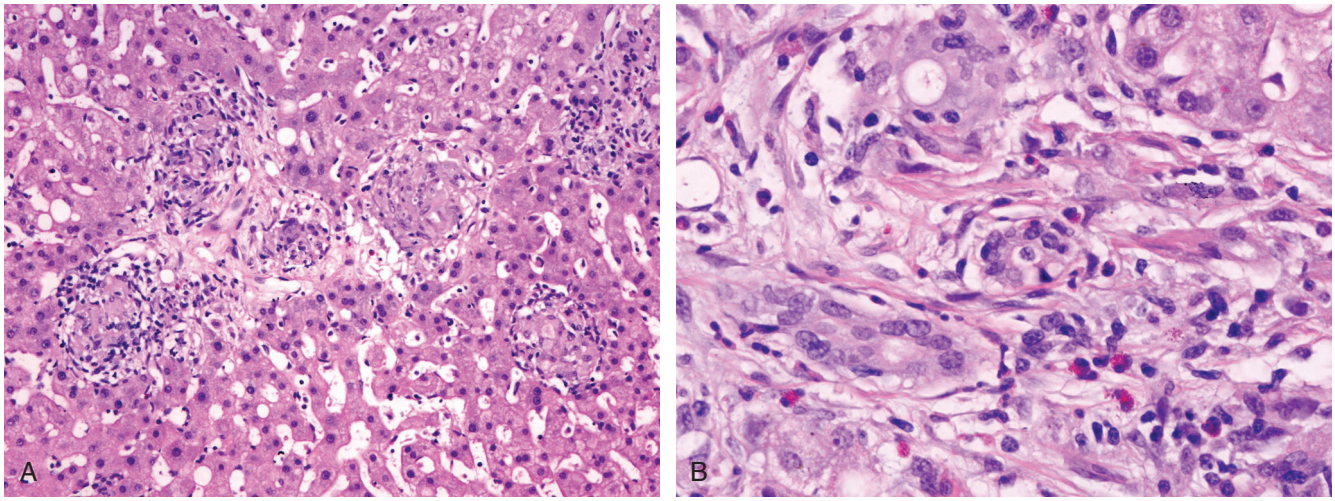

Figure 10-18. Liver biopsy in a patient with bacillus Calmette-Guérin infection. **A,** Several small granulomas are present in this view. **B,** In some portal tracts, bile duct injury and scattered eosinophils are present, suggesting a hypersensitivity reaction.

Table 10-2 Infections Associated with Granulomatous Inflammation in the Liver

Viral
Hepatitis C virus
Cytomegalovirus
Epstein-Barr virus
Mycobacterial
Tuberculosis
Leprosy
Atypical tuberculosis
Bacterial
Brucellosis
Cat-scratch disease
Enteric fever; typhoid fever
Listeriosis
Melioidosis
Tularemia
Whipple disease[134]
Pasteurella multocida[135]
Yersinia enterocolitica[136]
Actinomycosis
Nocardiosis
Rickettsial
Q fever
Chlamydial
Lymphogranuloma venereum
Psittacosis
Spirochetal
Syphilis
Lyme disease
Fungal
Aspergillosis
Blastomycosis
Candidiasis
Coccidioidomycosis
Cryptococcosis
Histoplasmosis
Mucormycosis
Paracoccidioidomycosis
Pneumocystis
Helminthic
Ascariasis
Capillariasis
Fascioliasis
Opisthorchiasis
Schistosomiasis
Strongyloidiasis
Visceral larva migrans
Protozoal
Leishmaniasis
Toxoplasmosis

it was seen more often in children.[137] More recently, biliary disease has emerged as a common etiology, and with that shift, the age of the patients has also increased, to 55 to 60 years of age.[138-140] Diabetes mellitus is a strong risk factor for the development of pyogenic liver abscess.[140,141] Other frequent comorbidities are malignancy, alcohol abuse, cirrhosis, hypertension, recent surgery, and immunosuppression.[138,139,142] A significant minority of cases remain cryptogenic. Although the disease carries a high mortality, improved diagnosis, abscess drainage, and antibiotic therapy have reduced the mortality rate to 5% to 31%.[138,142] Patients typically present with fever, chills, right upper quadrant pain, and elevated alkaline phosphatase.[138,139] Men are affected more often than women in most series.[138-140] Most abscesses are solitary; multiple abscesses occur in 25% to 45% of cases.[138-140,142] Most abscesses are right sided (55% to 70%), with left-sided and bilateral disease occurring less often.[137,138,140]

Culture of aspirated purulent material from the abscess or of blood may yield the offending organisms, although both of these are occasionally negative. Sometimes blood culture results do not correlate with pus culture results; therefore, blood culture alone is not sufficient to determine the etiology.[138] Depending on the organism, serology may be useful. The most commonly isolated organisms are *Escherichia coli, Klebsiella pneumoniae, Enterococcus, Streptococcus,* and *Pseudomonas* species.[138,139,142] A third of infections are polymicrobial (Fig. 10-19). Organisms that produce formic hydrogenlyase, such as *Klebsiella* spp. and *E. coli,* can convert acids that accumulate within the abscess to carbon dioxide and hydrogen gas; infection with these organisms can result in gas-forming pyogenic abscess, which carries a higher risk of septic shock, bacteremia, and mortality.[143] Abscesses secondary to *Yersinia enterocolitica* or *Yersinia pseudotuberculosis* are often associated with underlying hemochromatosis.[144-147] Anaerobes are isolated in up to 25% of cases, sometimes together with aerobes.[139,148,149] Microaerophilic streptococci, *Bacteroides fragilis*, *Fusobacterium necrophorum*, and *Clostridium* spp. are the most commonly implicated anaerobes. *Actinomyces* spp. are infrequently found by either anaerobic culture of aspirated pus or identification of filamentous bacteria and sulfur granules on histologic examination of resection material (Fig. 10-20); these organisms may be associated with the formation of sinus tracts.[150-153] Rarely, *Francisella tularensis*,[154] *Burkholderia pseudomallei* (the agent of melioidosis),[155,156] or *Listeria monocytogenes*[157] causes liver abscesses. Fungi, such as *Candida* and *Aspergillus,* are found in about 15% of cases.[148,158]

Complications of pyogenic liver abscess include metastatic infections such as endophthalmitis, meningitis, osteomyelitis, pyelonephritis, and pneumonia. The two main risk factors for metastatic infection are infection with *K. pneumoniae* and underlying diabetes mellitus.[142,159,160] Although surgical management was once the mainstay of therapy, percutaneous drainage and antibiotics have become the first-line approach.[138]

Acute Cholangitis

The term *acute cholangitis* refers to an infection of the bile ducts characterized by jaundice, abdominal pain, and sepsis, in combination with biliary obstruction. Bacterial colonization of the biliary tree in the absence of obstruction produces no symptoms; conversely, sterile obstruction of the bile duct produces a picture

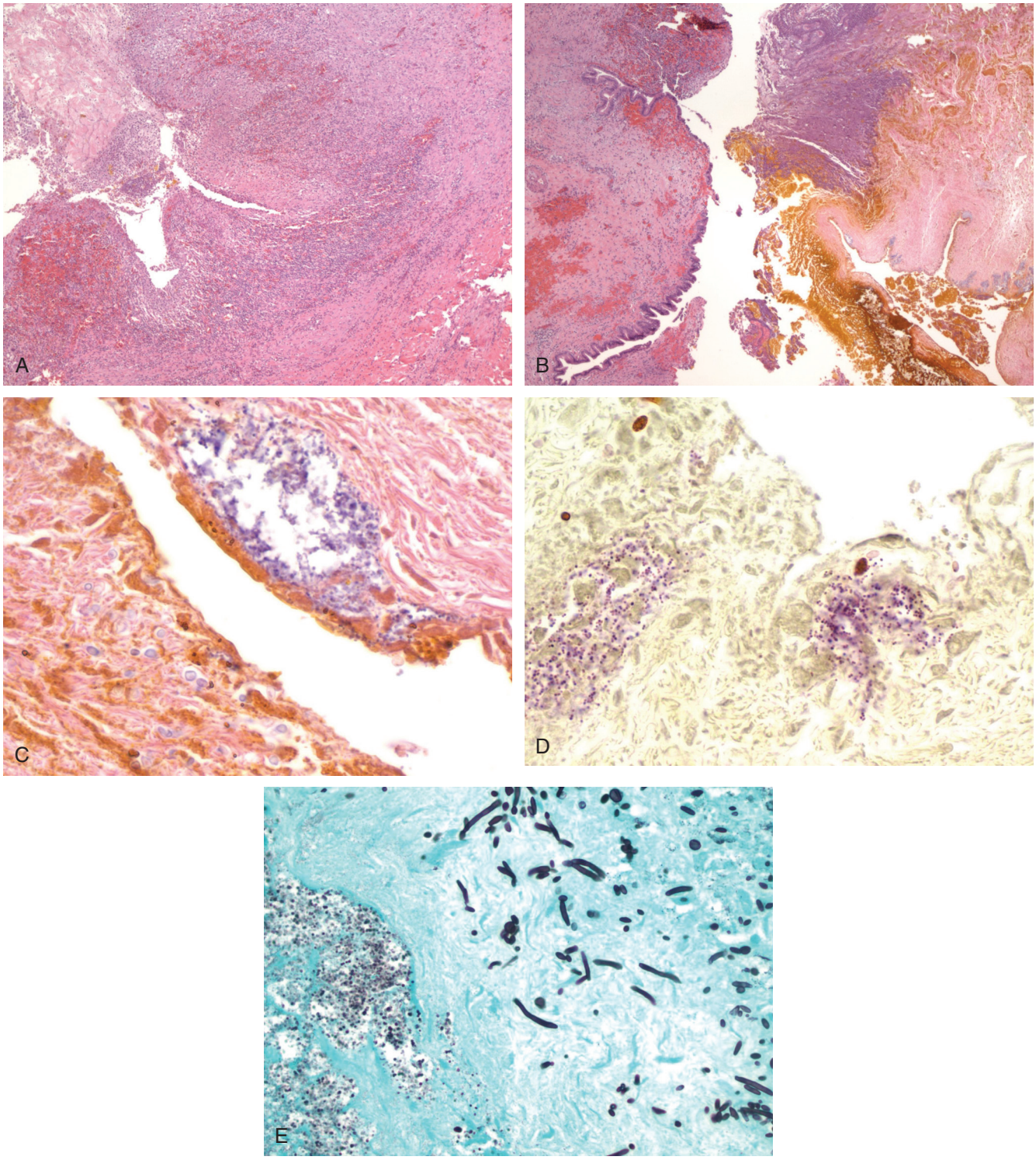

Figure 10-19. Hepatic abscesses arising from polymicrobial cholangitis with *Enterococcus* and *Candida* in a liver transplant recipient. **A,** The abscess contains a center of necrotic debris, fibrin, and neutrophils surrounded by granulation tissue and inflammation, with a fibrotic rim. **B,** In some areas, residual bile duct epithelium at the abscess edge betrays origin from cholangitis. **C,** Yeast forms *(lower left)* are present adjacent to bacterial cocci *(upper right)* in the bile duct lumen. **D,** Gram-positive cocci are revealed by Brown-Hopps stain. **E,** Yeast forms and pseudohyphae consistent with *Candida (upper right)* and bacterial cocci *(lower left)* are present (GMS stain).

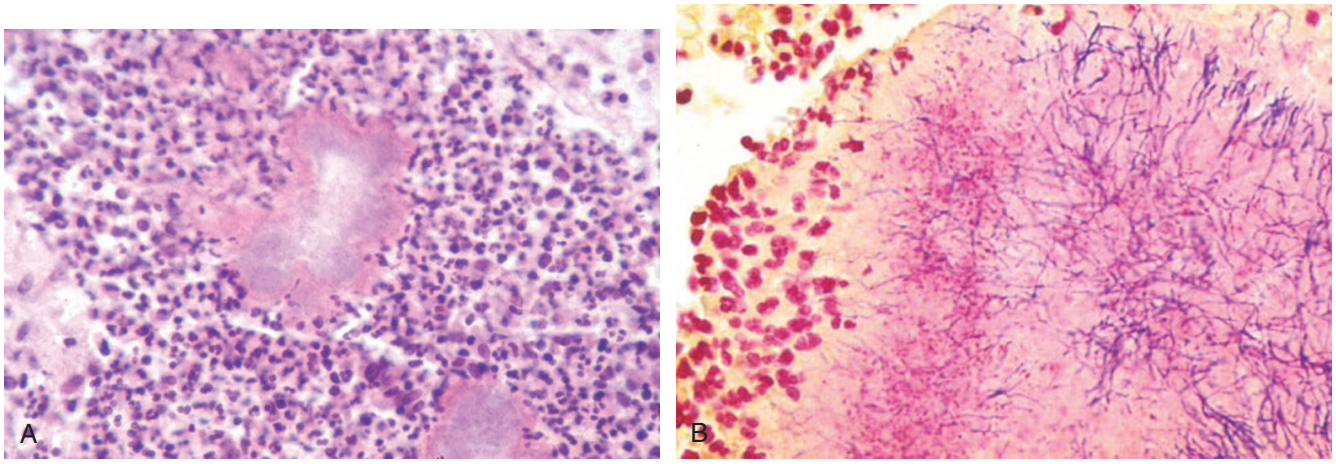

Figure 10-20. *Actinomyces.* **A,** Sulfur granule with aggregate of filamentous bacteria and neutrophils. **B,** Brown-Hopps stain shows gram-positive filamentous bacteria in the sulfur granule. (Courtesy of Dr. Laura Lamps.)

of aseptic obstructive jaundice.[161] The route by which bacteria colonize the bile ducts is uncertain. Possible sources include reflux of intestinal contents through the choledochal sphincter; passage from an infected gallbladder; and lymphatic, hepatic arterial, or portal venous bacteremia.[161] Obstruction is most often due to gallstones. Other causes include strictures, malignancy, and congenital anomalies of the ampulla of Vater. How bactibilia and obstruction leads to biliary septicemia is uncertain. Cholangiovenous reflux with increased intrabiliary pressure can be demonstrated using contrast, and higher biliary pressures are associated with an increased incidence of purulent bile, sepsis, and bacteremia.[161]

Manifestations of acute cholangitis range from mild, recurrent illness to overwhelming sepsis. Most patients are middle aged, and men and women are affected equally. Fever and jaundice are the most common symptoms. In 1877, Charcot proposed a clinical triad: right upper quadrant abdominal pain, fever, and jaundice.[162] About 70% of patients present with the full triad. Reynolds arrived at a pentad in 1959 by adding hypotension and delirium.[163] Although rare, the pentad describes patients with high mortality risk.[164] Alkaline phosphatase and bilirubin are elevated in most patients, but blood cultures are positive in fewer than half of patients.

The bacteria that infect the biliary tree usually derive from the gut. The bacteria most commonly isolated from bile are *E. coli, Enterococcus, Klebsiella, Proteus, Pseudomonas,* and *Enterobacter.*[161,165] Improved culture techniques have shown a significant incidence of infection by anaerobes, such as *B. fragilis* and clostridial species, frequently in association with previous biliary-intestinal anastomosis, an elderly patient, and more severe illness.[161,166] Overall, 56% of cases are polymicrobial. Mycotic infection of the bile duct, principally by *Candida albicans*, is rare and affects older patients, patients with malignancy, immunosuppressed patients, and diabetics.[161]

The histology of acute cholangitis is similar to that of large duct obstruction, with portal edema, neutrophilic portal and periductal inflammation, and neutrophils within duct epithelium.[167,168] In some cases, neutrophils accumulate within the duct lumina; although this is suggestive of infection, the association is not sufficiently reliable to be predictive.[167,168] Microabscesses and macroscopic abscesses may be seen. Thrombophlebitis may result in portal vein thrombi.[168] Patients suffering from shock may show necrosis of the liver.[168] Chronic changes include strictures, dilatations, portal fibrosis, and. potentially. ductopenia. Histologic findings frequently do not correlate with clinical status, in that most cases of acute cholangitis show relatively minor histologic changes, and patients with mild symptoms can have frank abscesses.[168] Histology is also not predictive of survival.[164] Therefore, clinical and microbiologic correlation is frequently required to make the diagnosis of acute bacterial cholangitis.

Most patients respond well to antibiotics. The efficacy of a specific antibiotic depends on its biliary secretion, which is affected by the size of the compound. The inflammatory process also can cause impairment of secretion. Treatment of the obstruction is necessary to prevent recurrence. Some patients require emergent biliary drainage in addition to antibiotics, and there may be a survival advantage to surgical management of the obstruction.[164] Complications of acute cholangitis include renal failure and the development of hepatic abscesses.[161]

Recurrent Pyogenic Cholangitis (Oriental Cholangiohepatitis)

Recurrent pyogenic cholangitis is a disease that historically was seen largely in the Far East but is reported in increasing numbers in the West, largely among Asian immigrants. The disease is characterized by abdominal pain, fever, chills, and jaundice resulting from recurrent attacks of suppurative cholangitis associated with intrahepatic biliary stones.[169] The cause is not fully known, but bacterial infection of the biliary tree is perhaps the inciting event. Enteric organisms, particularly *E. coli*, are cultured from bile in most cases.[169] Bacteria deconjugate bilirubin glucuronide, which then precipitates with calcium in the bile as soft, brown, friable calcium bilirubinate stones.[169,170] Exactly what predisposes patients to biliary tract infection is unknown, but the geographic distribution of this disease mirrors that of *Clonorchis sinensis* and *Ascaris lumbricoides,* and biliary parasites are detected in a significant minority of patients.[169] Dead flukes and ova within the bile ducts, accompanied by bile stasis, may lead to bacterial infec-

tion. However, large numbers of people in endemic areas are infested with liver flukes without recurrent pyogenic cholangitis. In any case, the recurrent cholangitis results in intense periductal inflammation and fibrosis, strictures, and dilated ducts filled with sludge.[170] Morphologically, large ducts show chronic and acute cholangitis, fibrosis, and peribiliary gland hyperplasia. Pigmented stones and pus are seen in ducts; liver abscesses may be present.[169] Bile ductular proliferation with cholangiolitis and periductal fibrosis develops. Cholangiocarcinoma is a complication.

Brucellosis

Brucellosis largely affects handlers of livestock, particularly those in the meatpacking industry. Most patients present with an acute illness characterized by malaise, fever, chills, sweats, weight loss, and headache, but some patients become symptomatic after many years of dormancy or are episodically symptomatic.[171] Viral illness or trauma may precipitate relapse of chronic brucellosis.[171] The most common histopathologic pattern is granulomatous hepatitis.[172,173] In a series of 14 patients with brucellosis, all had hepatic granulomas in both portal tracts and lobules.[174] These granulomas may be indistinguishable from TB or sarcoidosis, and brucellosis should be considered in any patient with hepatic granulomas.[173] The presence of granulomas does not reliably distinguish among the various species of *Brucella,*[175-178] despite a report that *Brucella melitensis* is not associated with granulomas.[179] Other findings may include nonspecific acute hepatitis with hepatocyte necrosis, inflammation, and Kupffer cell hyperplasia.[171,174,178]

Rarely, patients present with a mass mimicking a tumor in the liver or spleen, known as a brucelloma.[171,180] In one series of 15 patients with brucelloma in the liver or spleen, half had suffered from brucellosis many years before, suggesting reactivation of latent disease.[181] Radiologically, brucellomas have central calcification with peripheral necrotic areas.[171,180,181] Histologically, a brucelloma shows necrotic areas surrounded by a palisaded granulomatous reaction.[180,181]

Hepatic pyogenic abscess due to *Brucella* is rare and may be associated with *Brucella suis.*[171] The diagnosis is established by *Brucella* agglutination titer or culture, although the latter is difficult.

Bartonella (Cat-Scratch Disease)

Cat-scratch disease is a self-limited infection caused by infection with *Bartonella* spp. after inoculation by a cat, which usually manifests as a local skin reaction and lymphadenopathy. Most cases are attributed to *B. henselae,* but *B. quintana* has been implicated in some.[182] Approximately 1% to 2% of patients with *Bartonella* infection develop severe systemic disease with involvement of the liver, spleen, bone, central nervous system, or lung.[183] Most patients with hepatosplenic presentation are children 5 to 10 years of age.[182,184,185] Patients often have nonspecific symptoms, including fever, abdominal pain, chills, headache, malaise, and weight loss. About 25% of patients have lymphadenopathy, but often the classic skin papule of cat-scratch disease is absent.[182-184] Hepatic lesions are typically multiple and associated with abdominal lymphadenopathy and, in some cases, splenic lesions; many patients come to biopsy to exclude neoplasia.[183,185,186] On laparotomy, the liver may be found to be studded with hard nodules of varying sizes.[186]

The hallmark lesion in hepatic cat-scratch disease is an irregular, stellate microabscess surrounded by a layer of palisading histiocytes, lymphocytes, and a rim of fibrous tissue (Fig. 10-21).[183,186] Younger lesions may show more necrosis with less organization of the inflammatory granulomatous response, whereas older lesions may show confluent granulomas with scarring and scant residual necrosis.[183] These hepatic lesions are similar to the ones seen in lymph nodes in patients with cat-scratch disease, but they have also been noted in infections with *Y. enterocolitica, F. tularensis,* lymphogranuloma venereum, mycobacterial species, *Candida*, and *Actinomyces.*[183] Other lesions may appear as small. rounded granulomas with giant cells and small foci of central necrosis, similar to caseating granulomas in mycobacterial or fungal infections. The background liver parenchyma shows sinusoidal dilatation, portal mixed but predominantly lymphocytic inflammatory infiltrates, portal fibrosis,

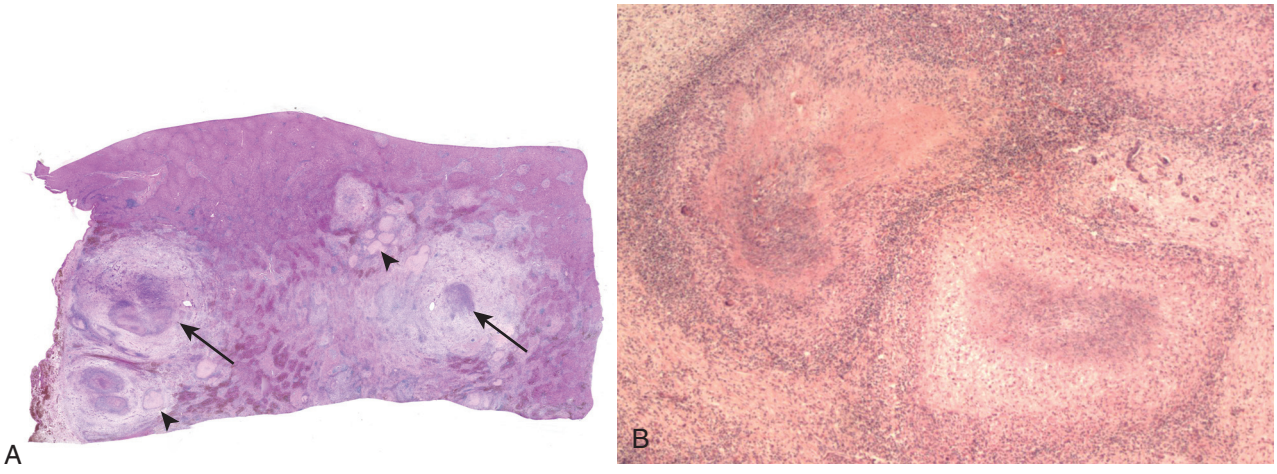

Figure 10-21. Cat-scratch disease involving the liver. **A,** Low-power view of a section of liver shows multiple stellate abscesses *(arrows)* and several older, hyalinized scars *(arrowheads).* **B,** Medium-power view of stellate abscesses shows central necrosis surrounded by palisaded histiocytes, chronic inflammation, and fibrotic tissue.

periductal concentric fibrosis, and focal bile ductular proliferation.[183] These changes are attributed to mass effect and are also seen in other infections that result in space-occupying lesions, such as pyogenic abscesses.[183]

Warthin-Starry stains identify bacilli in some cases, and the organisms often cluster around vessels or along collagen fibers; the stain is not specific for the organism.[184] Culture is difficult. The diagnosis can be confirmed by PCR and Southern blot for *Bartonella* DNA on tissue, skin testing, or serology.[182,183,187] The disease is self-limited without long-term hepatic dysfunction. The infection responds dramatically to rifampin, erythromycin, or doxycycline, but antibiotics are unnecessary in most cases.

Bartonella also may cause vascular proliferative lesions in the liver. Bacillary epithelioid angiomatosis is a vasoproliferative tissue reaction to *B. henselae* or *B. quintana* that usually occurs in immunocompromised hosts. Hepatic involvement shows sharply demarcated periportal areas in which the normal parenchyma is replaced by vascular tissue with extravasated erythrocytes, delicate spindle cells, neutrophils, and karyorrhexic debris, mimicking Kaposi sarcoma.[91] Similar lesions have been designated as bacillary peliosis hepatis; these are characterized by the presence of multiple blood-filled cystic spaces, foci of necrosis, fibromyxoid stroma, and clumps of granular purple material that correspond to organisms on Warthin-Starry stain and electron microscopy.[92] The latter lesions can be mistaken for nonbacillary peliosis hepatis. Although these infections can be progressive and fatal, they respond to antibiotics.

Enteric Fever (Typhoid and Paratyphoid Fever)

Enteric fever (the inclusive term for typhoid and paratyphoid fever) is caused by infection with *Salmonella enterica* serotype Typhi (*S. typhi)* or serotype Paratyphi (*S. paratyphi*). The disease is transmitted via the fecal-oral route from food or water contaminated by an acutely ill person or a chronic carrier.[188] Human beings are the only known reservoir. Most infections today occur in countries where sanitary conditions are poor; the Indian subcontinent has a particularly high incidence.[188] Travelers to these areas can also be affected. Although *S. typhi* causes 80% of infections, *S. paratyphi* may be more important among travelers, possibly due to a vaccine effect that only protects against *S. typhi*.[188] In indigenous populations, enteric fever is a disease of young children and adolescents, whereas among travelers, the age of the patients reflects the age of travelers.[188]

Ingestion of the organism is followed by an asymptomatic period of about 7 days, during which the organism multiplies within mononuclear phagocytic cells in Peyer patches, mesenteric lymph nodes, liver, and spleen.[189] This is followed by a bacteremic phase, with fever, chills, headache, and rose spots. During this phase, invasion of the gallbladder occurs, either directly or from infected bile. Chronic biliary carriage occurs in 2% to 5% of cases, even after treatment, particularly among women, the elderly, and patients with cholelithiasis.[188,189] In these cases, shedding of virus continues for more than a year and is a public health risk. The majority of patients experience minor degrees of hepatomegaly and elevated transaminases. However, the presentation can resemble acute viral hepatitis, with very high transaminases or even fulminant hepatic failure, although coinfection with HAV or HEV may be responsible for some of these cases.[188] Intestinal perforation, hemorrhage, and encephalopathy are the most important complications. The diagnosis is made by blood culture or Widal serology assay.

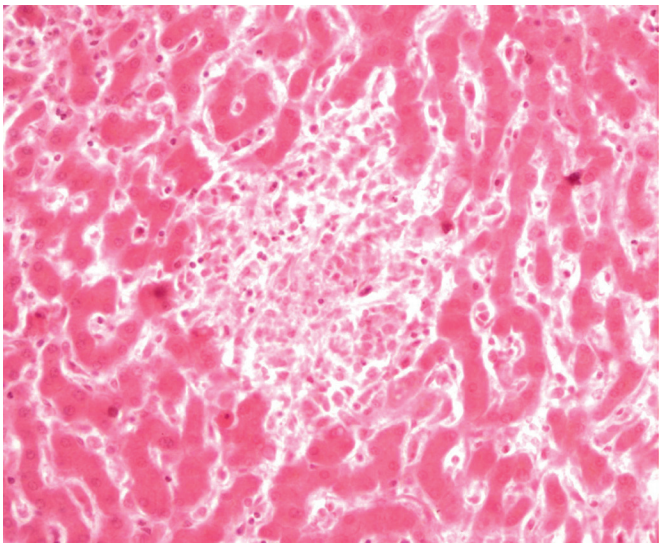

Figure 10-22. Typhoid nodule in typhoid fever. An aggregate of mononuclear cells, including histiocytes and lymphocytes, is present in the lobule. The surrounding liver shows prominent Kupffer cells in the sinusoids.

In the liver, hyperplasia of the reticuloendothelial system results in prominence of mononuclear cells in the sinusoids and typhoid nodules (Fig. 10-22).[190,191] Typhoid nodules are lobular collections of macrophages that ingest bacteria, erythrocytes, and degenerated lymphocytes.[191] These nodules may resemble granulomas but are not true epithelioid granulomas, although granulomatous hepatitis has been described as well.[192] Abscesses are rare.

Tularemia

Tularemia is caused by the coccobacillus *Francisella tularensis.* The disease is most often transmitted to humans by ticks or by animal contact, especially with rabbits. Inhalation outbreaks have been associated with lawn mowing and brush cutting in contaminated areas.[154] Most patients have pulmonary involvement. Other features include fever, cutaneous ulcers, lymphadenopathy, headache, and malaise. Hepatic involvement occurs in up to 75% of patients and includes hepatosplenomegaly and mild to moderate elevations of transaminases.[193] Severe cases may show jaundice. Liver histology shows suppurative microabscesses and areas of necrosis (Fig. 10-23). As the lesions age, they become more granulomatous.[194] The diagnosis is often established serologically, because the organism is difficult to culture and is rarely seen on tissue Gram stain. PCR assays for *F. tularensis* in fresh tissue and on formalin-fixed tissue have been described.[154]

Melioidosis

Melioidosis is a glanders-like disease caused by *B. pseudomallei*, a gram-negative aerobic bacillus that survives within phagocytic

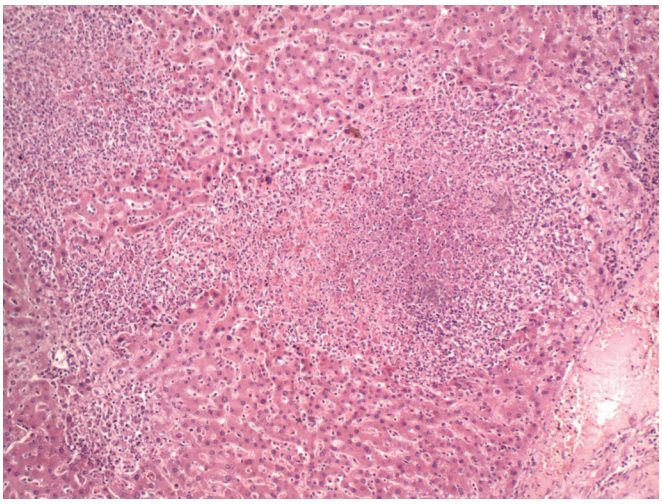

Figure 10-23. Tularemia involving the liver. Several small abscesses are present throughout the lobules.

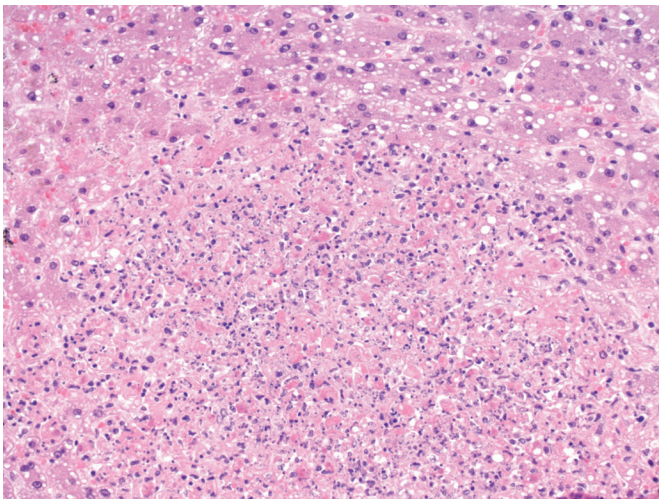

Figure 10-24. Liver from a patient who died of systemic listeriosis, showing microabscess and steatosis in the surrounding hepatocytes.

cells. The organism is a soil saprophyte that prefers wet soils and is an important community-acquired pathogen in Southeast Asia and northern Australia, particularly during rainy seasons.[156] Percutaneous inoculation and inhalation are modes of transmission. Travelers can be exposed when they come in contact with wet soil, such as during adventure tours.[195] Occasionally, patients have chronic disease or reactivation of a latent focus years after leaving an endemic area, a possibility that caused concern for veterans returning from Vietnam.[195] Predisposing factors include diabetes mellitus, renal disease, alcoholism, cirrhosis, and immunosuppression.[155,156] The acute form of the disease is characterized by abscess formation, predominantly in the lung, but seeding and abscess formation also occur in the liver, spleen, skeletal muscle, and lymph nodes; often, multiple sites are involved.[155,156,196] Chronic melioidosis shows granulomatous inflammation with central irregular abscesses, indistinguishable from the stellate abscesses of cat-scratch disease, tularemia, or lymphogranuloma venereum.[196] The granulomas may show caseous-type necrosis, mimicking TB.[196] The lesions in chronic melioidosis are usually confined to a single organ. Serology is not completely reliable, but *B. pseudomallei* can be readily cultured from abscess material.[155]

Listeriosis

Listeria monocytogenes is a gram-positive, facultative intracellular bacillus that is an occasional contaminant of food, even despite proper refrigeration. Infection is associated with pregnancy, extremes of age, diabetes mellitus, and immunosuppression. Transplacental transmission causes granulomatosis infantiseptic-um, which is characterized by abscesses and granulomas in various fetal organs.[197] After ingestion, the organisms invade the Peyer patches and are transported to the liver, where they are cleared from the bloodstream by Kupffer cells. Some organisms escape from Kupffer cells and invade hepatocytes, where, protected from the host immune response, they replicate. Neutrophils are recruited to the area, forming abscesses, and after a few days, granulomas form in an attempt to impede further spread. Once the organisms escape the granulomas and are released into the blood, they have a predilection for the central nervous system and placenta.[197]

Hepatic involvement can manifest as solitary liver abscess, multiple liver abscesses, or hepatitis (Fig. 10-24).[157,197] Solitary liver abscess is associated with diabetes mellitus, absence of bacteremia or extrahepatic manifestations, and a relatively good prognosis.[157,197] Multiple liver abscesses are more often associated with bacteremia, extrahepatic sites of involvement, and meningitis and carry a worse prognosis.[157,197] Diffuse hepatitis is associated with underlying conditions such as viral hepatitis, pregnancy, or alcohol abuse.[197,198] Bacteremia is highly likely in cases with diffuse hepatitis. The histology is that of chronic active hepatitis with extensive necroinflammatory activity and occasionally granulomas.[198] The diagnosis is made by culture of the organism from blood or abscess material.

Spirochetes

Syphilis

Treponema pallidum infection can affect the liver in secondary syphilis, in tertiary syphilis, or congenitally. Involvement by the liver in secondary syphilis has been reported in men and women. Several cases have been reported among homosexual men,[199-203] possibly from portal transport of the organism after anal intercourse.[203] A characteristic clinical picture is cholestatic jaundice, hepatomegaly, and a disproportionately elevated alkaline phosphatase level.[199,201,202,204-206] The trademark palmar rash of syphilis may be the key to diagnosis.[204,205] Histologic examination of liver may show a variety of pathologic patterns. In most cases, portal inflammation with mononuclear cells or neutrophils surrounding damaged bile ducts (pericholangitis) is the main finding.[200,201,206,207] Scattered foci of necrosis may be present in the lobules, sometimes accompanied by inflammation around the central veins and Glisson's capsule.[201,203,207,208] Granulomatous hepatitis is described in some cases (Fig. 10-25).[208,209] Spirochetes are only rarely identified in histologic sections with silver stains such as Warthin-Starry or Steiner.[199,204,207]

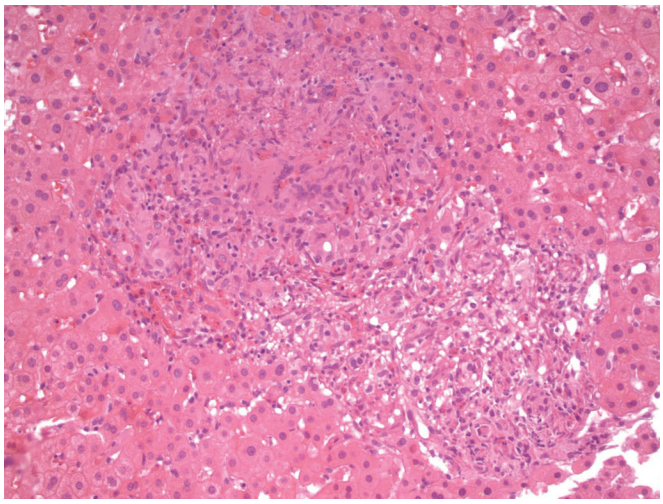

Figure 10-25. Secondary syphilis in the liver. Granulomatous inflammation is seen adjacent to an inflamed portal tract.

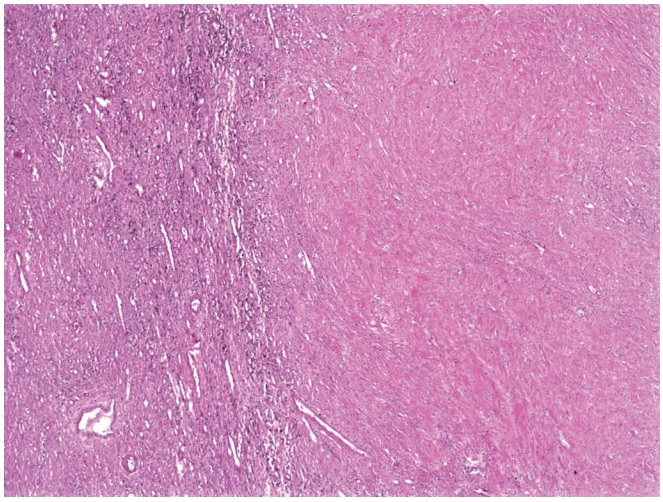

Figure 10-26. Old gumma in the liver, showing a hyalinized nodule with mild chronic inflammation at the periphery. (Courtesy of Dr. Laura Lamps.)

In tertiary syphilis, multiple gummas in the liver may mimic metastatic carcinoma.[210] Histologically, gummas resemble TB, in that they are composed of masses of granulomas with caseating necrosis, surrounding fibrosis, chronic inflammation, and histiocytic inflammation.[210] Healed gummas may be replaced by fibrous scars (Fig. 10-26). Retraction of these scars can distort the liver by producing pseudolobules or so-called hepar lobatum.[210] Scars near the hilum may result in portal hypertension.

Congenital syphilis is frequently fatal, but surviving infants may have hepatomegaly and jaundice, with diffuse fibrosis. Spirochetes can be seen within connective tissue septa, parenchymal cells, and the walls of small vessels.[211]

Leptospirosis

Leptospirosis is an acute febrile illness caused by *Leptospira interrogans* that affects humans and animals in all parts of the world.[212] The disease is biphasic, with a septicemic phase followed by an immune phase with antibody production and urinary excretion of the organism.[212] Most patients experience a mild anicteric illness, with fever, headaches, and myalgias. Severe cases, characterized by hepatic, renal, and pulmonary involvement, are known as Weil syndrome.[212] Liver pathology is predominantly a cholestatic hepatitis with reactive hepatocellular changes and Kupffer cell hyperplasia.[191,212,213] Scattered Councilman bodies, bile within canaliculi, and mild portal inflammation may be seen.[191,214] Very rarely, spirochetes can be demonstrated on silver stain. The diagnosis is based on serologic assays.

Lyme Disease

Lyme disease is caused by *Borrelia burgdorferi* and is transmitted by *Ixodid* ticks, usually during the months of May through October. Hepatomegaly and symptoms of hepatitis are uncommon. Elevated transaminases indicate mild hepatocellular injury, although a nonhepatic source is possible in the case of Lyme disease–associated myositis.[193] In the liver, mononuclear cells, plasma cells, and granulocytes are seen in sinusoids. Kupffer cell hyperplasia, steatosis, and hepatocyte ballooning are also described.[193,215] Granulomatous hepatitis is uncommon; necrotizing granulomas have been reported.[216] Organisms are only rarely seen in hepatic sinusoids and parenchyma with silver stain such as Dieterle.[215]

Rickettsia

Q fever (*Coxiella burnetii*)

Q fever is a zoonotic rickettsial disease that is caused by the aerosol spread of *Coxiella burnetii* from infected sheep and cattle. The disease is endemic in the southwestern United States and in southwestern Ontario. Most patients suffer an acute, self-limited infection that typically manifests as pneumonitis, although chronic infection with endocarditis is well known. Unlike other rickettsial diseases, Q fever does not produce a rash.[217] Hepatic involvement is common, and the disease may even manifest as hepatic disease without pulmonary symptoms.[218] The diagnosis is established by complement-fixing antibodies to phase II *C. burnetii* antigen in serum.

The classic lesion of Q fever is the fibrin ring granuloma, which can be found in liver or bone marrow (Fig. 10-27).[217-222] Also known as donut or ring granulomas, these lesions contain a central fat vacuole that can lead to their being mistaken for lipogranulomas, but on closer inspection a ring of fibrin surrounds the fat vacuole. The fibrin ring is highlighted on trichrome stain. Q fever is the most commonly reported etiology, but fibrin ring granulomas have also been reported in other infectious and in noninfectious conditions, including hepatitis A,[8,9] *Staphylococcus epidermidis* infection,[223] allopurinol hypersensitivity,[224-227] visceral leishmaniasis,[226,227] giant cell arteritis,[228] CMV,[75] EBV,[70,229] Hodgkin disease,[227,230] toxoplasmosis,[226] and Boutonneuse fever.[226]

In addition to fibrin ring granulomas, epithelioid granulomas with or without central necrosis may be seen and can be mistaken for TB.[217,221,226,231] Other findings in Q fever hepatitis

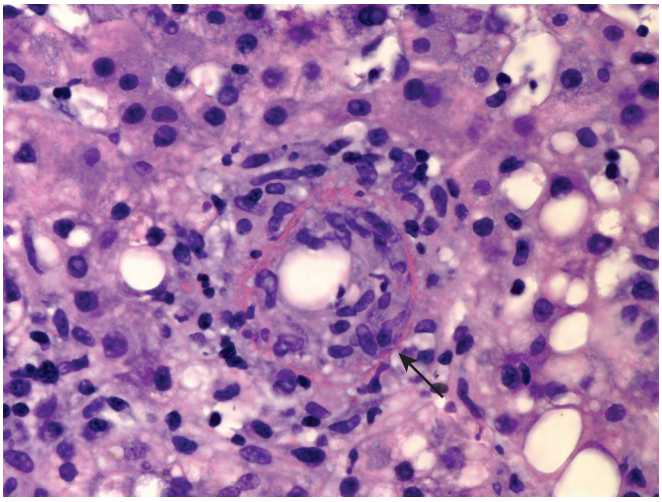

Figure 10-27. Fibrin ring granuloma. A collection of histiocytes contains a central fat droplet surrounded by a rim of histiocytes, a ring of fibrin *(arrow)*, and another rim of histiocytes.

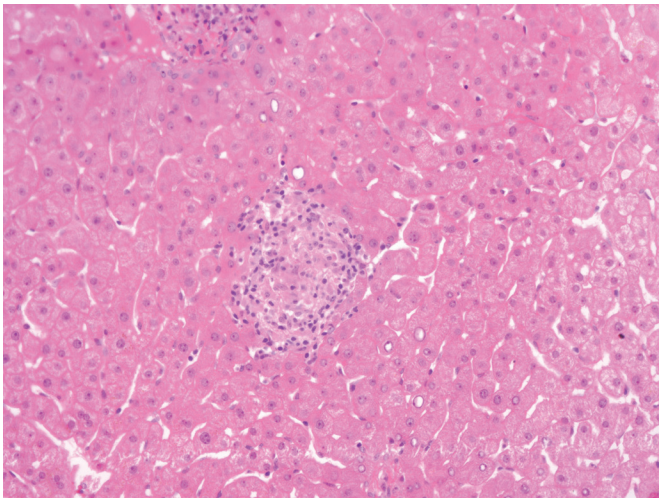

Figure 10-28. Liver biopsy sample in an immune-competent patient with hepatic and splenic histoplasmosis. A solitary, well-formed granuloma is present in the liver.

include moderate steatosis, focal liver cell necrosis, Kupffer cell hyperplasia, hemosiderin deposits, and, rarely, microabscesses.[221]

Ehrlichiosis

Ehrlichiosis is caused by gram-negative obligate intracellular organisms that are transmitted by a tick vector, predominantly in the southeastern United States. Human monocytic ehrlichiosis is caused by *Ehrlichia chaffeensis* and *Ehrlichia canis*, whereas human granulocytic ehrlichiosis is caused by *Ehrlichia phagocytophila* and *Ehrlichia equi*.[193] Symptoms include fever, headache, anorexia, and myalgia. The relatively low incidence of rash (20%) contrasts with the frequent presence of a rash in Lyme disease and Rocky Mountain spotted fever.[232,233] Transaminases are often mildly elevated, although they may be in the range of viral hepatitis. Alkaline phosphatase and bilirubin are less likely to be elevated, but may be so with severe cholestasis.[232,233] Liver biopsy may show lobular lymphohistiocytic aggregates and sinusoidal infiltration by lymphohistiocytic cells associated with erythroleukophagocytosis.[234] In cholestatic cases, bile stasis, duct epithelial injury, and neutrophilic infiltration of medium-sized ducts may suggest extrahepatic obstruction.[232,234] Other reported findings include focal hepatic necrosis, steatosis, granulomas, and foamy Kupffer cells with scattered apoptotic bodies.[233,234]

Rocky Mountain Spotted Fever

Rickettsia rickettsii is transmitted by the wood tick, *Dermacentor andersoni,* in the Rocky Mountain region and by the dog tick, *Dermacentor variabilis,* in the eastern United States. Mild to moderate transaminase elevations and occasionally jaundice may be seen. The main pathologic lesion is vasculitis, and rickettsiae are capable of infecting the endothelial lining cells or portal blood vessels, especially arteries and arterioles, and sinusoidal lining cells.[193,235] Reports of autopsy livers describe portal inflammation, portal vasculitis with subendothelial and intramural mononuclear leukocytes, portal vascular thrombi, portal tract hemorrhage, sinusoidal leukocytosis, and erythrophagocytosis by Kupffer cells.[235,236] Immunofluorescence techniques can be used to identify the organisms in tissue.

Boutonneuse Fever

Boutonneuse fever is caused by *Rickettsia conorii* and is transmitted by the dog tick. The disease is found in Mediterranean countries between the months of June and September. Hepatic involvement shows Kupffer cell swelling and increased sinusoidal cellularity. Small foci of hepatocyte necrosis are seen, associated with collections of histiocytes, a few neutrophils, and lymphocytes.[237,238] The mononuclear cell aggregates in the areas of necrosis may resemble poorly formed granulomas, but they are not true epithelioid granulomas.

Fungi

Histoplasma

Histoplasma is considered to be the most common fungal cause of hepatic granulomas, and it is a common cause of granulomatous hepatitis in areas where *H. capsulatum* is endemic, such as in the Ohio River valley.[239] In one series from that region, 15 (65%) of 23 children with hepatic granulomas had histoplasmosis demonstrated by PCR.[240] In another series, 50% of liver biopsy specimens with granulomas cultured positively for *Histoplasma*. Although histoplasmosis is usually self-limited in infants or immunocompromised patients, it can manifest with progressive disseminated disease requiring treatment.[240] Progressive disseminated histoplasmosis often involves the liver, with hepatomegaly in 62% of patients and abnormal liver function studies in 84%.[241]

Histologically, the appearance is identical to sarcoidosis, with numerous well-formed epithelioid granulomas (Fig. 10-28).[115]

In immunocompromised hosts, loose collections of histiocytes with numerous intracellular organisms can mimic leishmaniasis (Fig. 10-29). The absence of a kinetoplast on Giemsa stain helps distinguish *Histoplasma* from *Leishmania*.[242] The diagnosis can be established with methenamine silver staining of involved tissue, fungal culture, or complement fixation tests.[241]

Candida

Candidiasis is especially problematic in immunocompromised patients, particularly those with leukemia or cytotoxic chemotherapy-related neutropenia.[243] *Candida* accounts for 62% to 91% of fungal infections in the liver transplantation population, affecting 5% to 42% of all liver transplant recipients.[72] Patients present with fever, abdominal pain, and elevated alkaline phosphatase; blood cultures are negative in at least half of the cases.[244] Usually, patients are in the recovery phase from the neutropenic episode, suggesting a role for the host inflammatory response in defining the lesions.[243] The diagnosis is often not made until postmortem examination.

Radiologically, the lesions appear targetoid and, in the case of older lesions, calcified.[243,244] Grossly, the liver and spleen are studded with white to yellow nodules. In the early stages, the nodule consists of a necrotic center and surrounding neutrophilic infiltrate. Periodic acid–Schiff (PAS) or Gomori methenamine silver (GMS) stains demonstrate yeast or pseudohyphae in the center of the abscess. As the lesion matures, a palisaded histiocytic reaction may develop at the periphery of the lesion, surrounded by a fibrous wall (Fig. 10-30).[244] Eventually, well-defined granulomas with giant cells may be seen.[243] As the lesions progress with increasing fibrosis, organisms become more difficult to detect, so their absence does not exclude the diagnosis. The adjacent liver parenchyma frequently shows sinusoidal dilatation,

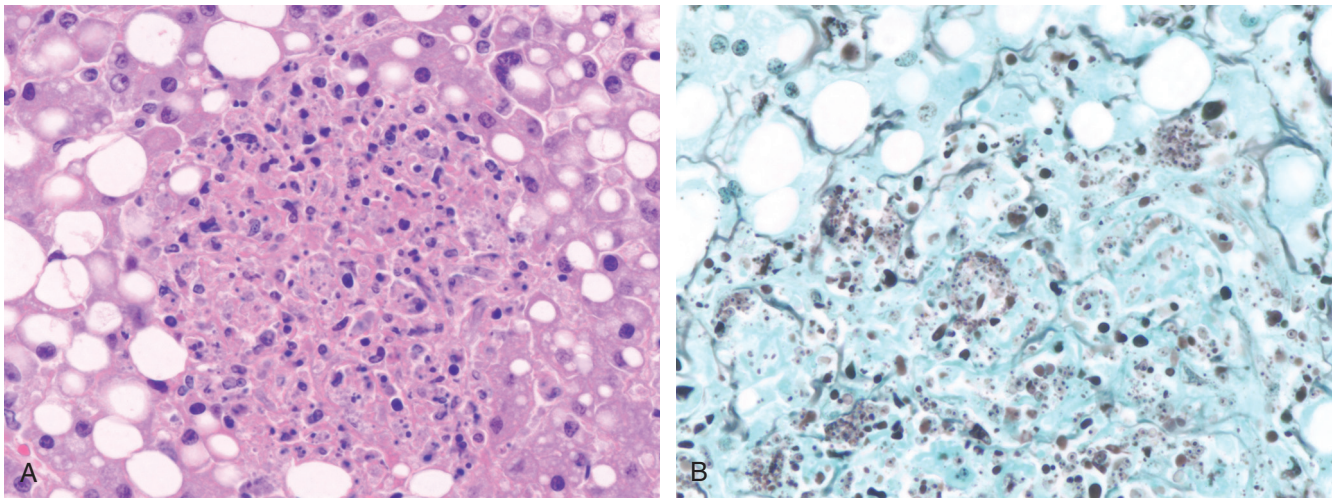

Figure 10-29. Histoplasmosis in an AIDS patient. **A,** Necrotic lesions are composed of histiocytes and debris. **B,** GMS stain shows yeast in macrophages in the necrotic lesion.

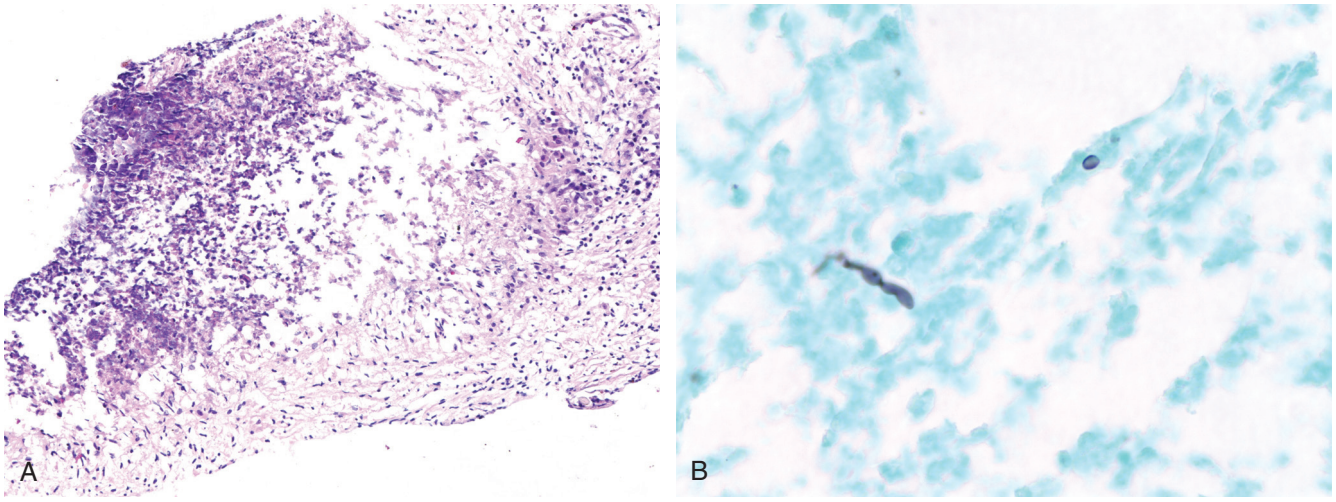

Figure 10-30. Candidal abscess in a patient with leukemia. **A,** Abscess with necrosis and neutrophils *(upper left)* surrounded by a palisaded histiocytic reaction. **B,** Rare yeast and pseudohyphae on GMS staining.

portal edema, neutrophilic infiltrate, and ductular reaction, presumably due to mass effect.[244] Candidal infection of the biliary tree and gallbladder occurs in disseminated candidiasis, with bacterial cholangitis, or as isolated candidal cholangitis or cholecystitis.[245,246]

Pneumocystis jiroveci

Pneumocystis jiroveci (formerly *Pneumocystis carinii*) is a fungal organism that typically causes lung infections in immunocompromised patients. Extrapulmonary infection is rare but has been associated with the use of prophylactic aerosolized pentamidine, which suppresses pulmonary disease but might allow for dissemination of the organism.[247,248] Grossly, the liver is studded with yellow-white nodules. The pathology ranges from caseating granulomas to massive infiltration of sinusoids and vessels by the organism with little inflammatory reaction (Fig. 10-31).[247,248] The organism appears as indented, helmet-shaped "cysts" on silver stains.

Aspergillus

Aspergillus fumigatus involving the liver is seen in cases of disseminated aspergillosis and in immunosuppressed patients. Liver abscess and cholangitis secondary to *Aspergillus* infection have been described.[158,249] The organism is easily demonstrated on methenamine silver or PAS stains and shows characteristic septate hyphae with acute-angle branching.

Zygomycetes

Fungi of the class Zygomycetes are ubiquitous in nature, occurring in decaying material and soil. The members of this class most often implicated in human disease are *Rhizopus, Rhizomucor, Mucor,* and *Absidia*.[250] Hepatic zygomycosis has been reported in immuno-compromised patients, in patients receiving chemotherapy, in stem cell transplant recipients, and in solid organ transplant recipients.[250-254] Hepatic infection in the absence of pulmonary disease may be caused by spread from a gastrointestinal source.[250] These fungi have broad (10 to 20 μm), aseptate or hyposeptate, ribbon-like hyphae with right-angle branching, and they have a propensity to invade blood vessels, leading to extensive necrosis, infarctions, and dissemination.[250-253] Diagnosis requires identification of the fungus in tissue or culture. However, tissue culture sensitivity is poor, possibly because the grinding of tissue in preparation for plating destroys the delicate hyphae, and this technique is no longer recommended.[250] Blood cultures are always negative. In tissue identification, erroneous classification as *Aspergillus* may occur if the hyphae are hyposeptate.[250]

Penicilliosis

Penicilliosis is an infection caused by the dimorphic fungus, *Penicillium marneffei,* which is endemic in Southeast Asia.[255] This pathogen has emerged as the third most common opportunistic infection among AIDS patients in Southeast Asia and southern China, although it affects people with apparently normal immunity as well.[256] Pathologic findings include granulomatous inflammation with relatively few organisms, suppurative abscesses, and necrotic lesions consisting of histiocytes filled with organisms, the latter being typical in immuno-compromised patients.[255,256] The organisms appear as small spherules, 2 to 4 μm in diameter, along with some elongated and septate forms; they are highlighted with methenamine silver stain or by PAS stain with diastase digestion (Fig. 10-32).[255,256] The main differential diagnosis is *H. capsulatum*.

Cryptococcosis

Cryptococcosis is caused by the encapsulated yeast, *Cryptococcus neoformans,* and hepatic infection has been reported in both immunocompromised and immune-competent patients.[257,258] In the immune-competent cases, granulomas are seen, whereas in

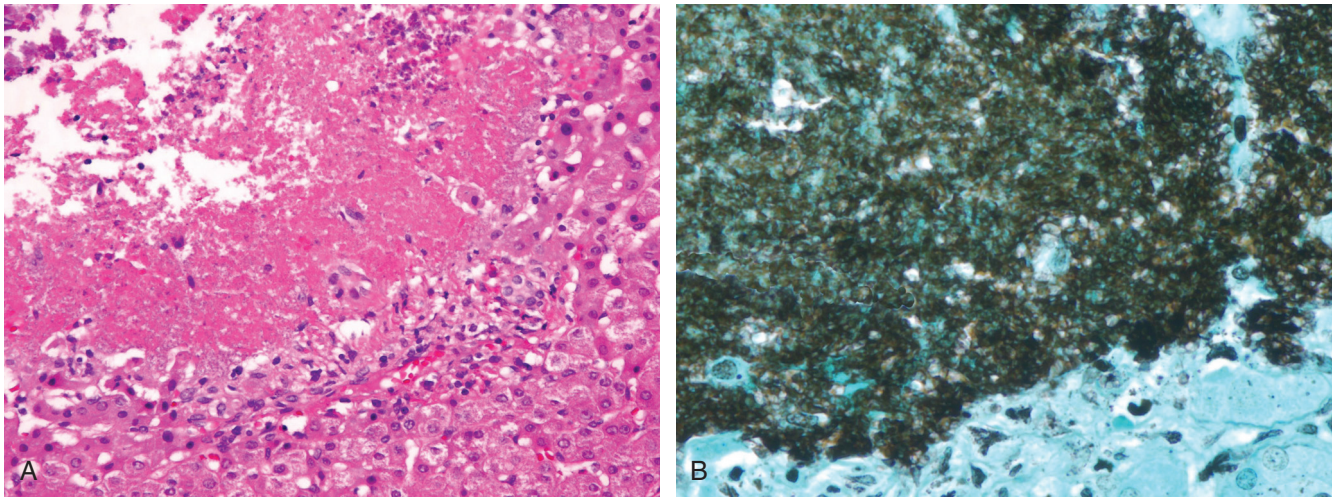

Figure 10-31. *Pneumocystis jiroveci* in the liver. **A,** Necrotic lesion composed of granular eosinophilic material with mild histiocytic reaction at the periphery. **B,** GMS stain demonstrates that the granular material is composed of masses of *Pneumocystis* organisms.

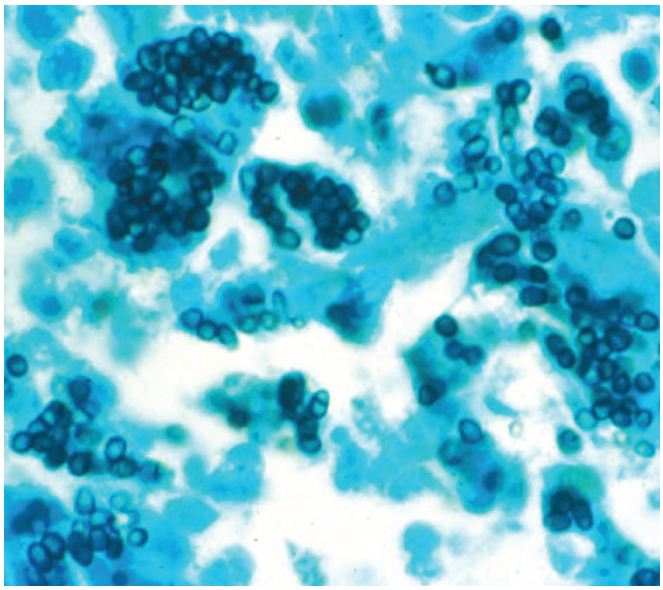

Figure 10-32. Penicilliosis. A GMS stain shows numerous yeast forms in macrophages. The organisms are round to oval, with a few slightly elongate and septate forms. (Courtesy of Drs. David Walker and Laura Lamps.)

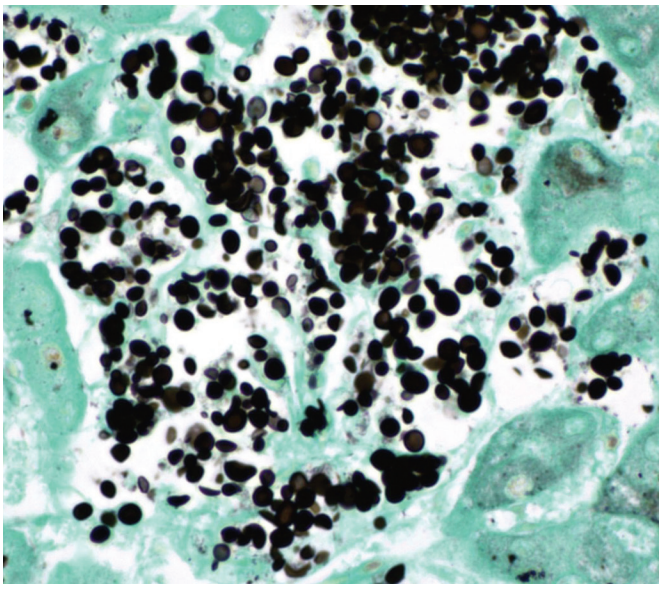

Figure 10-33. Capsule-deficient *Cryptococcus.* A GMS stain shows yeast cells of varying sizes within a collection of histiocytes in the liver. (Courtesy of Dr. Laura Lamps.)

AIDS patients, an inflammatory reaction is poorly developed. Autopsies in cases of disseminated infection have shown areas of necrosis with innumerable yeast cells, yeast cells diffusely within tissue admixed with cellular debris and inflammation, or yeast cells within Kupffer cells (Fig. 10-33).[259] Infection of the bile duct can mimic sclerosing cholangitis.[260] The organism can be demonstrated on silver stains, and mucicarmine stain can be used to highlight the capsule. The capsule is a virulence factor and is helpful in the diagnosis, but in rare instances, capsule-deficient strains can cause infection, particularly in immunocompromised patients (see Fig. 10-33). Capsule-deficient forms can be confused with other yeasts.

Coccidioidomycosis

Coccidioides immitis is endemic to the southwestern United States and northern Mexico. Disseminated infection can show granulomatous hepatitis or microabscesses containing the thick-walled spherules of *C. immitis,* which can be highlighted with PAS and methenamine silver stains.[261-263] The spherules may or may not contain endospores; immature spherules without endospores can be mistaken for *Blastomyces dermatitidis* or *C. neoformans.*[263] Serology and culture results can be used to establish the diagnosis.

Blastomycosis

Blastomyces dermatitidis is a dimorphic fungus that usually involves skin and lungs. The fungus is endemic to the southeastern and south central United States, the areas bordering the Great Lakes, and the Ohio and Mississippi River basins. Hepatic granulomas and cholangitis have been described.[264] Thick-walled yeast forms with broad-based budding are seen on PAS or silver stains (Fig. 10-34).

Paracoccidioidomycosis (South American Blastomycosis)

Paracoccidioides brasiliensis causes a chronic granulomatous disease known as South American blastomycosis. The disease is endemic in rural South America and affects males more often than females. Although pulmonary lesions are typical, extrapulmonary disease can occur. In the liver, the fungus usually causes a granulomatous reaction. Less often, it causes focal necrosis with neutrophilic exudates containing numerous organisms.[265]

Microsporidiosis

Microsporidia are obligate intracellular organisms that were originally believed to be primitive eukaryotes but have recently been reclassified as fungi based on DNA sequence data. Several species have been implicated in human disease. Infection of bile duct epithelium has been described as a cause of AIDS-related cholangitis.[95,97] A case of hepatitis has also been reported, with sinusoidal congestion and microgranulomas on light microscopy.[94] Electron microscopy is necessary to identify the organisms in most cases, but often the organism has already been identified in intestinal biopsy specimens by the time cholangitis develops.

Helminths

Schistosomiasis

Schistosomiasis is the second most common parasitic infection of humans after malaria. Several species of schistosomes affect humans: *Schistosoma japonicum* is associated with hepatic pathology more often than *Schistosoma mansoni.* The intermediate host is a population of snails that is not found in North America

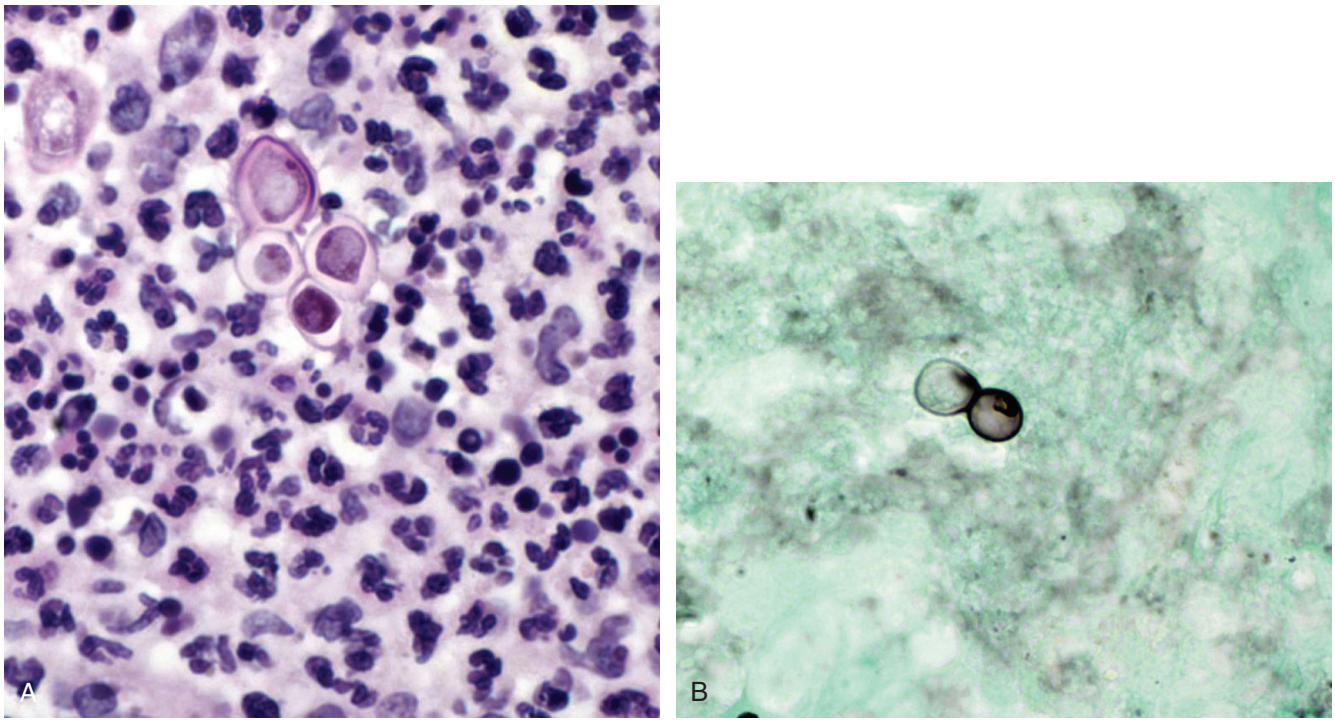

Figure 10-34. Blastomycosis. **A,** Broad-based, budding yeast forms are present in an area of suppurative inflammation. **B,** GMS stain shows broad-based, thick-walled yeast cells. (Courtesy of Dr. Laura Lamps.)

or Europe.[266] Infection occurs when the cercariae exit the snail and penetrate the skin of a vertebrate host. In the human host, the cercariae migrate to the lungs, where they mature, reach the left side of the heart, and then are carried to the portal hepatic circulation. In the mesenteric venous plexus, the male occupies the gynecophoric canal of the female, and the worms remain in a state of continuous copulation for their life span of 3 to 5 years.[266] Eggs released in the mesenteric venous plexus can migrate to the intestine (intestinal form) or into the liver (hepatosplenic form), where they lodge in the small portal vein tributaries. Granuloma formation around the eggs leads to pyelophlebitis and periportal fibrosis.

Histology shows portal fibrosis with partial or complete destruction of the main branches of the portal vein but sparing of arteries and ducts.[266] Adult worms metabolize large amounts of hemoglobin and regurgitate hemozoin pigment, which is engulfed by macrophages in the sinusoids and portal tracts and can be accentuated by Prussian blue stain. Despite the scarring, lobular architecture is maintained, so the fibrosis does not represent true cirrhosis. This pattern of fibrosis is known as Symmers pipe-stem fibrosis because of the clay pipe-stem appearance on gross pathology (Fig. 10-35).[266]

Eventually, portal hypertension supervenes with splenomegaly and esophagogastric varices. However, compensatory increase in hepatic arterial blood flow maintains hepatic perfusion and hepatic function.[266] Often, patients lack other stigmata of chronic liver disease. The diagnosis is based on the demonstration of ova in stool specimens. Serology to detect antischistosomal antibodies does not distinguish active from resolved infection. Enzyme-linked immunosorbent assays (ELISA) have been developed that detect schistosomal antigens in the serum and urine of actively infected patients. Antigen levels correlate with worm burden.[266]

Strongyloides

Strongyloides stercoralis exist as rhabditiform larvae in soil and as filariform larvae in humans. The organisms reside in the intestine, where they produce eggs that develop into rhabditiform larvae, which are shed in feces. In certain settings, rhabditiform larvae may develop into the infectious filariform larvae within the intestine; this form is capable of invading the intestinal mucosa and traveling throughout the body, typically the central nervous system, liver, and lungs. This unique cycle of autoinfection is accelerated in immunosuppressed patients. In the liver, the larvae can cause granulomatous hepatitis with or without larval remnants. The larvae measure between 6 and 13 μm, and they may be seen in sinusoids, portal tract lymphatics, or branches of the portal vein (Fig. 10-36).[267] Occasionally, the larvae do not provoke an inflammatory reaction.[267] Steatosis and cholestasis are additional features.

Enterobiasis (Pinworm)

Rarely, *Enterobius vermicularis* travels from the anus to unusual locations, such as the urethra or vagina. Rupture of the appendix or other intestinal disease may also provide the nematode with a mode of reaching the liver.[268] Subcapsular nodules in the liver may be found at the time of surgery; on histologic examination, they prove to be hyalinizing or calcifying granulomas

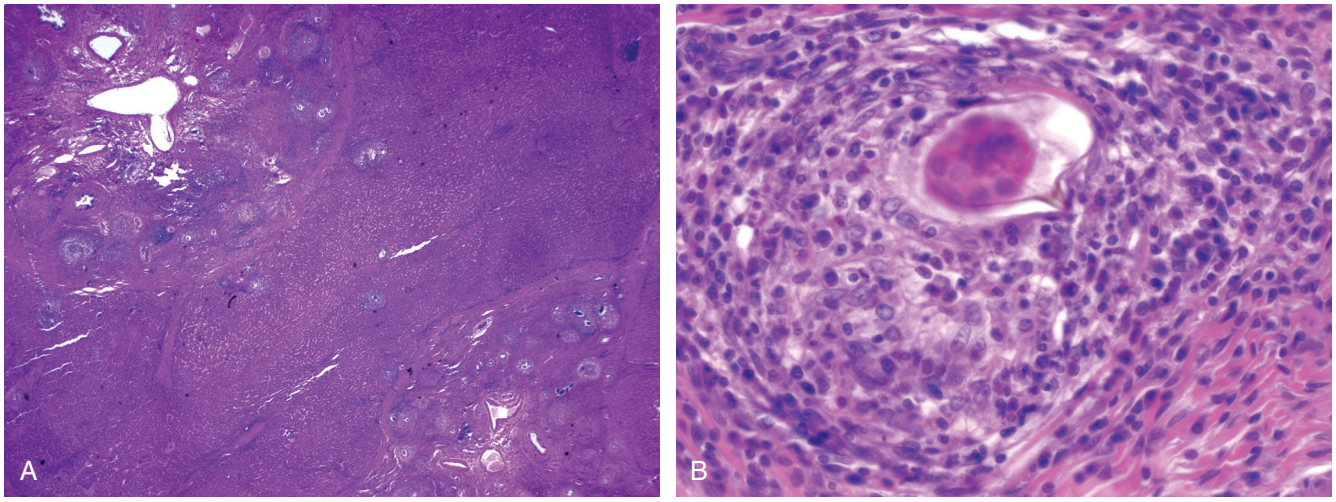

Figure 10-35. Schistosomiasis. **A,** The liver shows marked expansion of two portal areas with fibrosis and numerous granulomas, consistent with Symmers pipe-stem fibrosis. Note the absence of cirrhosis in the background liver. **B,** A high-power view of a granuloma surrounding a schistosome ovum with the characteristic lateral spine.

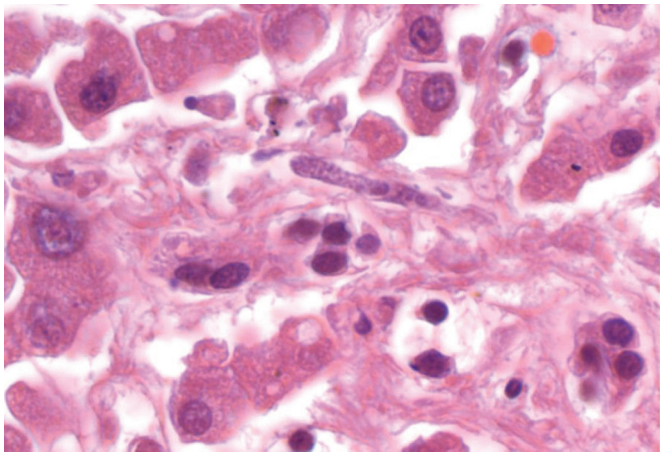

Figure 10-36. *Strongyloides* in an AIDS patient with disseminated *Strongyloides* infestation. A larval form is present in a small portal lymphatic channel.

containing remnants of pinworms with characteristic lateral alae and possibly ova.[268,269]

Echinococcosis

Echinococcosis or hydatid cyst disease is caused by species of the tapeworm, *Echinococcus*. *Echinococcus granulosus* is endemic in Mediterranean countries, Iran, India, China, Chile, and Argentina, whereas *Echinococcus multilocularis* is endemic in central Europe, the Near East, Russia, China, northern Japan, and Alaska.[270,271] The adult tapeworms live in the jejunum of dogs and other carnivores, the final hosts; the larvae infect herbivores, the intermediate hosts, when they ingest the eggs. Humans are incidental intermediate hosts, because further development of the cestode requires ingestion of the larvae by a carnivore.

Once ingested, the egg develops into a larval oncosphere, which penetrates the intestinal mucosa, enters the portal circulation, and, on reaching the target organ (usually liver or lung), forms a rounded, multinucleated mass that becomes cystic and progressively enlarges.[271] The hydatid cyst consists of an external, acellular, laminated cuticle and an inner germinal membrane that gives rise to brood capsules containing new larvae called protoscolices (Fig. 10-37).[271,272] Hydatid cysts form daughter cysts, either from the germinal membrane or from the protoscolices or brood capsules. In the case of *E. granulosus*, the cysts are slowly enlarging masses that remain asymptomatic for a long period. Eventually, they may cause dull abdominal pain and a palpable mass.[246] About 40% of cases are associated with complications, including erosion into bile ducts, through the hepatic capsule into the peritoneal cavity, into adherent organs, or through the diaphragm.[246] In alveolar hydatid disease due to *E. multilocularis*, the hepatic parenchyma is invaded and replaced by fibrous tissue with numerous embedded vesicles that mimics carcinoma.[270] Dense granulomatous inflammation, microcalcifications, and necrotic cavitation may be present.[272]

Alveolar hydatid disease carries a high mortality without surgery, due to liver failure, invasion of contiguous structures, or, less often, metastases to the brain.[270,272] Transplantation has been attempted, but there is a high risk of recurrence in the donor liver.[272] The diagnosis can be made radiologically and confirmed serologically, although some patients do not develop an immune response.[270,272]

Toxocara

Toxocariasis refers to infection by larvae of the dog ascarid, *Toxocara canis*, or, less commonly, the cat ascarid, *Toxocara cati*. In humans, these larvae do not develop into adult worms but travel throughout host tissue, primarily liver and lungs; therefore, the disease is known as visceral larva migrans.[273] Humans acquire the infection by ingesting the eggs from contaminated soil or by eating raw animal tissue (e.g., cow liver), that is infected by the encapsulated larvae. The larvae are released in the intestines, burrow through the intestinal wall, and reach the liver via the

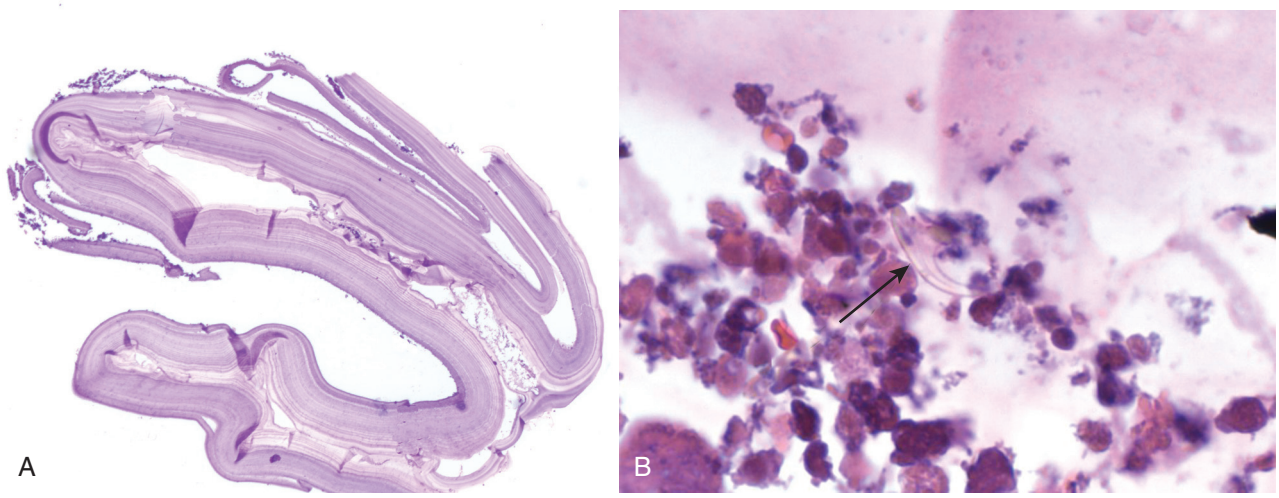

Figure 10-37. Echinococcal cyst. **A,** Collapsed cyst wall is composed of an acellular laminated cuticle. **B,** High-power view of a refractile hooklet *(arrow)* within cyst debris.

portal vein. From there, they travel to various other organs, causing eosinophilic inflammation, granulomas, and abscesses.[273] Most patients are asymptomatic but demonstrate peripheral eosinophilia. Vague abdominal pain, fever, cough, and dyspnea are occasional complaints.[273] Radiologic studies show multiple, ill-defined, oval or angular lesions that improve or resolve spontaneously, similar to *F. hepatica*. Serology is used to detect IgG to *Toxocara* antigens.

In liver biopsy specimens, multiple granulomas and confluent granulomas may be the main finding.[274,275] Grossly, the liver may show 0.3- to 1-cm, white-gray lesions, primarily in the subcapsular region of the right lobe.[276,277] These granulomatous lesions show central necrosis surrounded by a mixed inflammatory infiltrate that includes numerous eosinophils and palisaded granulomas. The central necrotic zone shows granular debris or eosinophilic material. Charcot-Leyden crystals may be seen in the areas of necrosis. Remnants of parasites are found in a minority of cases and measure 15 to 21 µm in diameter.[276] The differential diagnosis includes other causes of visceral larva migrans, including *Capillaria hepatica* and *Ascaris*.

Capillariasis

Capillaria hepatica mainly affects rodents but is also found in carnivores. The organism requires only a single host, with the liver containing both the adult parasite and its ova.[278] Eggs are deposited in soil, where, under favorable conditions, they embryonate. Ingestion of the unembryonated eggs does not result in hepatic disease but only in abdominal discomfort; in these spurious cases, eggs are passed in the stool. Ingestion of embryonated eggs results in hepatic disease and is not associated with passage of eggs in the stool.[278] Infection of humans is rare; children are more commonly affected, probably because of frequent soil-to-mouth contact.[278] Patients present with chronic fever, hepatomegaly, and peripheral eosinophilia. Liver biopsy specimens may show granulomas and eosinophils. Granulomatous lesions with central eosinophilic necrosis rimmed by palisaded histiocytes and numerous eosinophils similar to toxocariasis may be seen.[276] Remnants of the parasite and its eggs may be identified.[278] The parasite measures 50 µm or larger in diameter.[276] The elliptical eggs are 54 to 64 µm by 29 to 33 µm and have bipolar plugs.[278]

Fascioliasis

Fasciola hepatica and *Fasciola gigantica* are trematode bile duct flukes found primarily in sheep and cattle.[270,279] The leaf-shaped worms reach a size of about 2 cm and may remain viable in the bile ducts for more than a decade. The eggs pass in feces, hatch in water, and infect lymnaeid snails.[270] Snails release a cercarial stage of the parasite that contaminates aquatic plants that are ingested by sheep, cattle, or humans. Watercress is often associated with human infection.[280] Once ingested, metacercariae penetrate the intestine, traverse the peritoneal cavity, and penetrate the liver capsule.[281] They burrow through the liver parenchyma for 1 to 3 months, while maturing, and finally enter the bile ducts to complete the life cycle.

Acute (invasive) fascioliasis manifests with fever, right upper quadrant discomfort, hepatomegaly, and eosinophilia.[279] Infrequently, patients experience respiratory, cardiac, or neurologic symptoms that are believed to be immune-allergic in origin, because the organism only rarely appears at these sites.[279] As the flukes course through the liver, they create tracks of necrosis infiltrated by eosinophils, sometimes surrounded by a reaction of palisaded histiocytes (Fig. 10-38).[280,281] These tracks appear as yellow-white subcapsular nodules or cords at laparoscopy.[280,281] As the lesions age, they become cavities bound by granulation tissue, fibrous tissue, and calcifications.[281] Immature flukes that fail to reach the liver may produce ectopic abscesses, most often in the skin.[279]

Once the flukes penetrate ducts, egg production initiates chronic (obstructive) fascioliasis, characterized by local inflammation, fibrous thickening of the duct wall, ascending cholangitis, episodic biliary pain, and obstructive jaundice.[279] Peripheral eosinophilia is mild or absent in this stage. The flukes attach to

the bile duct epithelium using suckers and cause ductal epithelial proliferation, possibly due to their production of proline.[281] Large necrotic granulomas can develop around entrapped eggs, and tissue eosinophilia is typical in these lesions. Adult flukes can be found in the bile ducts or gallbladder, along with stones, hypertrophied muscle coat, and mucosal hyperplasia. Cholangiocarcinoma is not associated with fascioliasis. Diagnosis is made with serologic and antigen-identification tests or stool examination for ova, although the latter is useful only in chronic disease and may be negative if ova production is intermittent.[279]

Clonorchiasis

Clonorchis sinensis, Opisthorchis viverrini, and *Opisthorchis felineus* are similar and are usually considered together. *C. sinensis* infects persons in China and east Asia and is common among immigrants to New York City. *O. viverrini* is limited to Thailand, Laos, Vietnam, and Cambodia, and *O. felineus* infects cats and humans in parts of Russia and eastern Europe.[282,283] These bile duct flukes are acquired through ingestion of raw fish containing the metacercariae.[282,283]

The flukes migrate into the ducts via the ampulla of Vater, where they mature in about 25 days.[282,283] The adults reside in medium-sized and small intrahepatic ducts, and occasionally in the extrahepatic ducts, gallbladder, or pancreatic duct, where they can live for a decade or longer.[282] Human hosts excrete eggs that hatch in water, pass through snails and fish, and infect other humans or animals. Patients are usually asymptomatic but may present with abdominal pain, hepatomegaly, and eosinophilia or with the syndrome of recurrent pyogenic cholangitis.

Grossly, focal dilatation of segments of smaller ducts may be seen, with thickened walls and possibly worms in the lumen. The left lobe is affected more often, because the left intrahepatic bile duct is straighter and wider, allowing easier access for the worms. Bile ducts that harbor these flukes show dilatation, irregular thickening, adenomatous epithelial hyperplasia, and variable eosinophilia (Fig. 10-39).[282] Eggs are not usually seen in tissues. Ascending cholangitis, usually from *E. coli,* can lead to purulent exudates in dilated ducts. Bile duct obstruction can result from the worms, strictures, or calculus formation.[282] Stones often have dead worms as their nidus. Diagnosis is made by identifying the ova in stool or by ultrasonography. Patients are at risk for cholangiocarcinoma, which is often intrahepatic, multicentric, and mucin-secreting. Serology does not distinguish between present and past infection. Therefore, the diagnosis of active infection may require the detection of ova in stool.[282]

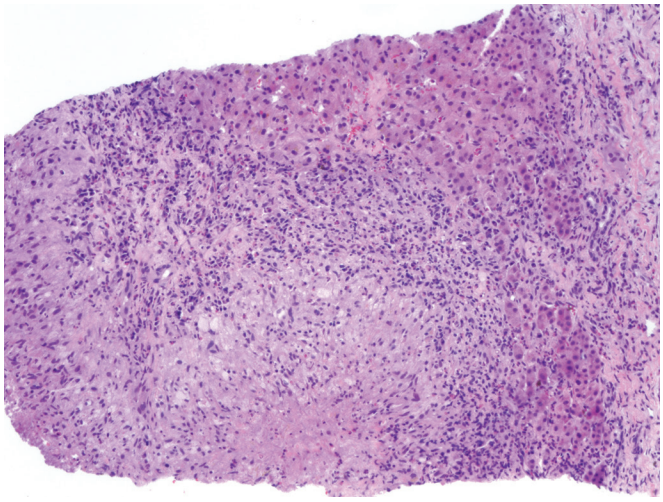

Figure 10-38. Fascioliasis. Necrotic tract is surrounded by a palisaded histiocytic reaction in a patient with *Fasciola* infestation.

Ascariasis

Ascaris lumbricoides rarely causes biliary ascariasis when the roundworms ascend the bile duct; this occurs usually in patients who live in endemic areas, have biliary abnormalities, or have undergone sphincterotomy. Although children are infected with *Ascaris* commonly, biliary involvement is rare in children, probably because of the narrow ampulla of Vater and bile duct

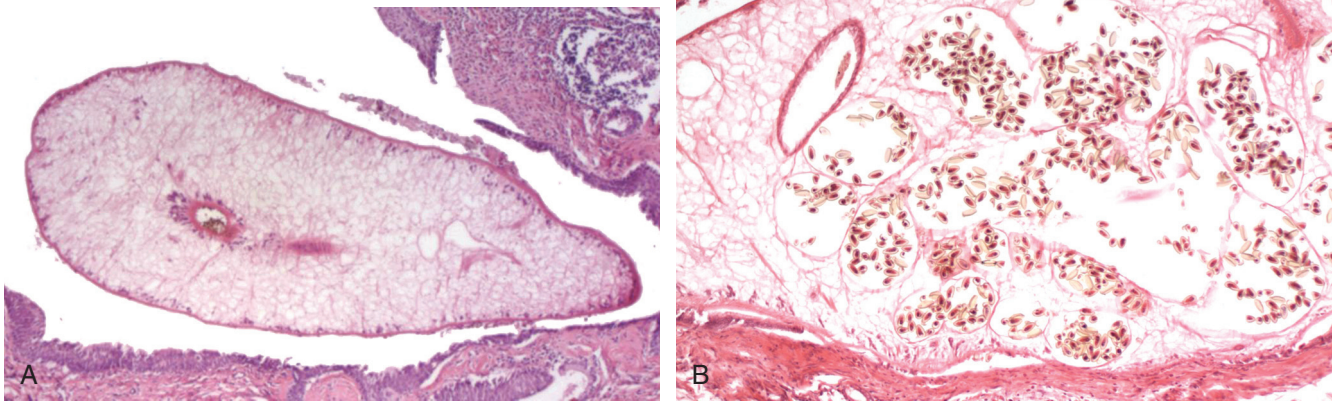

Figure 10-39. *Clonorchis* infestation. **A,** A fluke is present within a large duct that shows squamous metaplasia and periductal chronic inflammation. **B,** Higher magnification shows cross-sections of the uterus filled with ova.

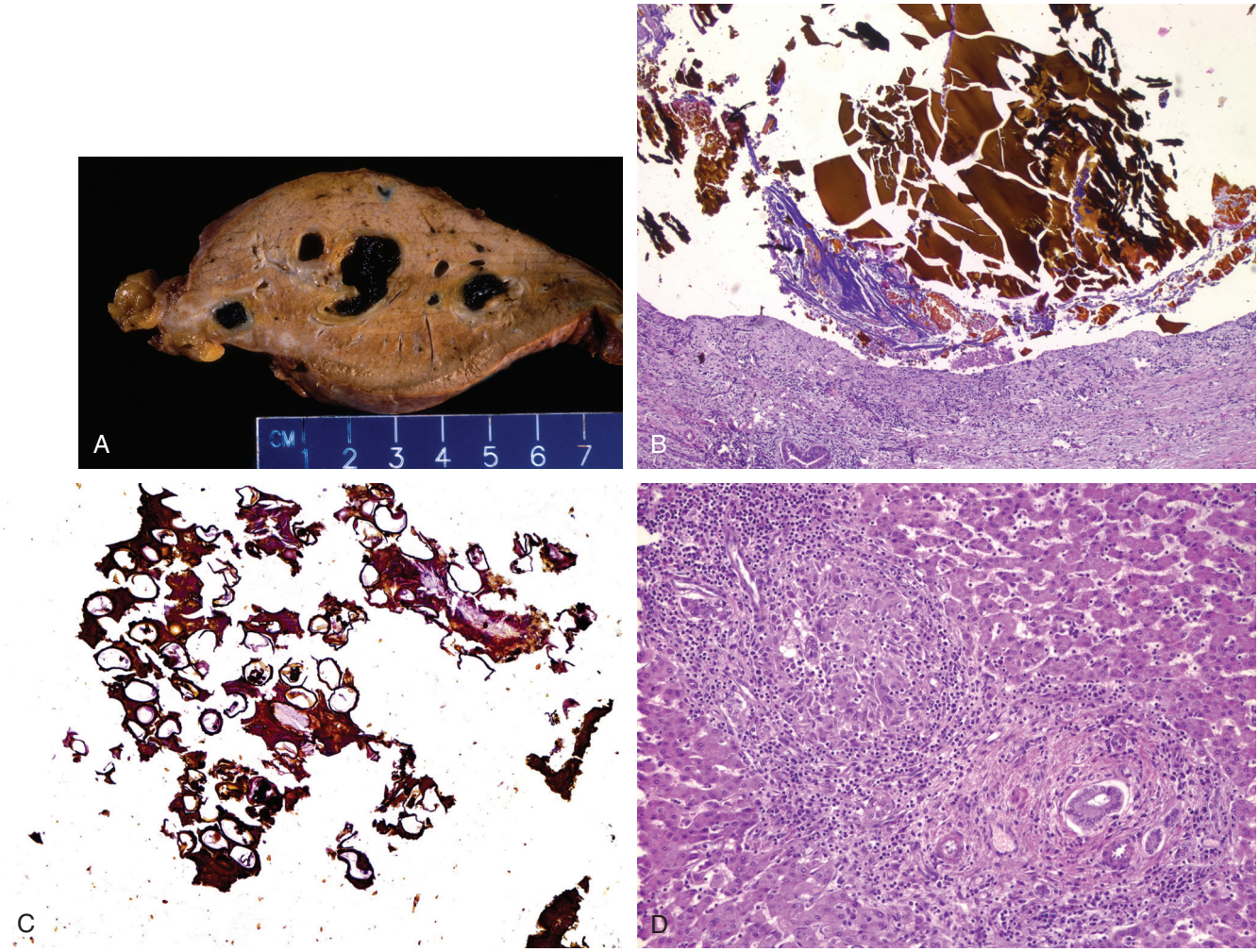

Figure 10-40. *Ascaris* infection in a patient with the clinical diagnosis of recurrent pyogenic cholangitis. **A,** Gross photograph of a section of liver shows dilated bile ducts inspissated with darkly stained sludge. **B,** On microscopic examination, the inspissated sludge is found to contain laminated, bile-stained structures suggestive of dead *Ascaris*. **C,** Focally, a collection of *Ascaris* ova is present in the sludge. **D,** Elsewhere in the liver, granulomatous inflammation was seen in the lobules adjacent to portal tracts.

lumen.[284] Bile duct infestation manifests as biliary colic, obstructive jaundice, or pancreatitis. Dying worms, in conjunction with *E. coli* and other bacteria that they transport into the liver, can cause suppurative cholangitis, liver abscesses, or the syndrome of recurrent pyogenic cholangitis (Fig. 10-40).[167] The worms can also penetrate liver tissue (visceral larva migrans), perforate Glisson's capsule, and exit into the subdiaphragmatic space.[167] The ova can cause granulomas and pseudotumors.[285] Ultrasonography can identify worms within the gallbladder or extrahepatic ducts or the presence of a dilated common bile duct.[284] Ova or adult worms can be found in stool in 91% of patients.[284] In some patients, the worms exit the ducts spontaneously; in others, anti-helminthic therapy or surgery is required.[284]

Protozoans

Amebiasis

Liver abscess is the most common extraintestinal manifestation of amebiasis. Amebic liver abscesses most likely arise from hematogenous spread of the trophozoites, probably via the portal circulation.[286] Often, patients with liver abscess have no bowel symptoms, and stool microscopy is negative for *Entamoeba histolytica* trophozoites and cysts.[286] Patients may present years after travel to an endemic area with fever, right upper quadrant pain, and hepatic tenderness.

The histopathologic findings in hepatic amebiasis consists of well-circumscribed regions of dead hepatocytes, liquefied cells, and cellular debris. A rim of connective tissue with few inflammatory cells and amebic trophozoites surrounds the necrotic lesion (Fig. 10-41). The adjacent hepatic parenchyma is often completely unaffected.[286] The number of trophozoites may be surprisingly small relative to the size of the abscess. The diagnosis is often made by identification of a lesion in the liver in the setting of positive amebic serology.

Malaria

The *Plasmodium* parasite has a life cycle that involves both mosquitoes and humans. When the parasite is first transmitted to a

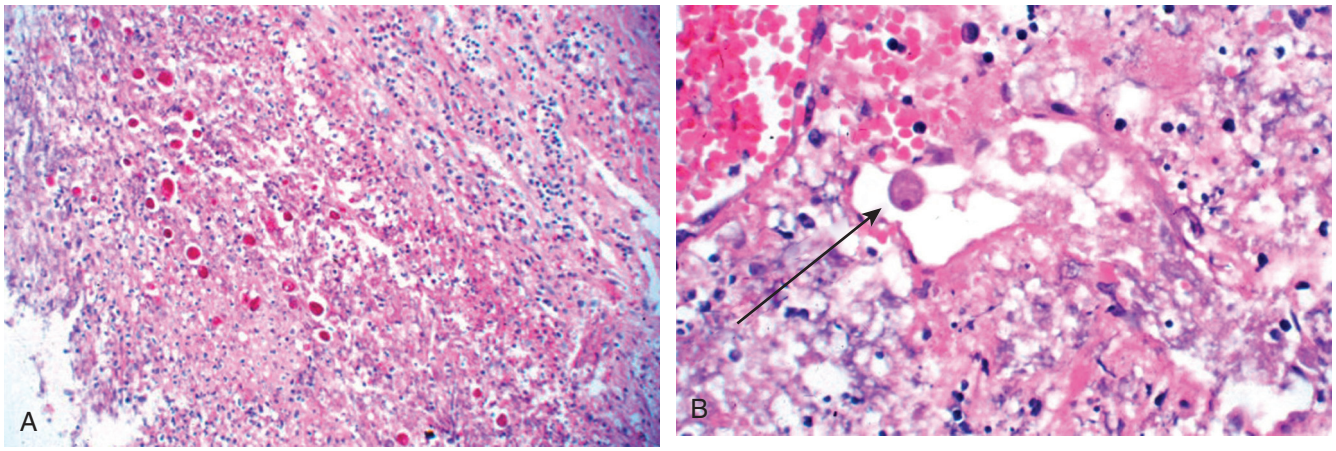

Figure 10-41. Amebic abscess in the liver. **A,** Low-power view shows the edge of an abscess cavity with inflammation and debris. **B,** High-power view of an amebic trophozoite *(arrow)* within the necrotic debris. (Courtesy of Drs. David Walker and Laura Lamps.)

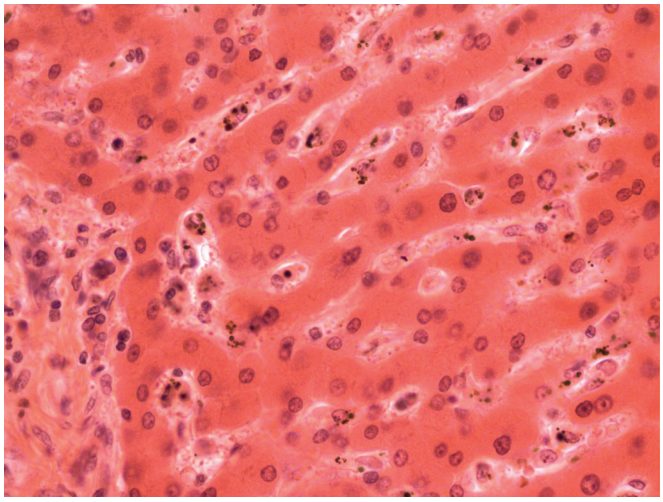

Figure 10-42. Malarial pigment within Kupffer cells.

human host, it is incapable of infecting red blood cells and must first pass through the liver. The parasite grows rapidly within hepatocytes, producing merozoites that can infect red blood cells. Through unknown mechanisms, the parasites render hepatocytes resistant to apoptotic signals.[287]

Hepatic dysfunction is well described in malaria, particularly with infection by *Plasmodium falciparum* or mixed infection with both *P. falciparum* and *Plasmodium vivax,* and usually involves mild abnormalities of liver function studies or jaundice.[288] Hepatic encephalopathy is rare. Hepatic dysfunction and jaundice may be multifactorial in etiology, including hemolysis, sequestration of infected red blood cells in sinusoids, or coexistent viral hepatitis.[288]

The histologic hallmarks of malarial hepatitis are varying degrees of hepatocyte injury and deposition of malarial pigment or hemozoin (Fig. 10-42). Inflammation is generally mild. Sinusoidal congestion and centrilobular necrosis may be caused by adherence of red blood cells in sinusoids, resulting in ischemia. Kupffer cell activation, fatty change, and cholestasis are other common findings.[288] Exoerythrocytic forms of the parasite in liver biopsy material can be demonstrated by immunofluorescence.[289]

Leishmania

Visceral leishmaniasis, or kala-azar, is caused by an obligate intracellular protozoan, *Leishmania donovani,* that is transmitted to humans by the sandfly, *Phlebotomus argentipes.* Worldwide, India has the highest incidence of kala-azar. Children comprise the majority of patients. In southwest Europe, visceral leishmaniasis affects adults, many of whom are coinfected with HIV.[290] In this population, the majority of patients are intravenous drug users, and the organism is transmitted by the sharing of syringes.[290] Also, reactivation of latent disease may occur in immunocompromised patients years after travel to endemic areas, making the infection difficult to suspect.[291] The organisms exist as flagellated promastigotes in the gut of female sandflies and as amastigotes in animal or human hosts. In visceral leishmaniasis, an incubation period of 10 days to 1 year is followed by low-grade recurrent fevers, malaise, wasting, anemia, and hepatosplenomegaly.[292] Death follows in 2 to 3 years, commonly from secondary infections.

The accumulation of mononuclear phagocytic cells in infected tissues leads to reticuloendothelial hyperplasia affecting the liver, spleen, intestinal mucosa, bone marrow, and lymph nodes.[292] In the liver, the typical pattern consists of marked hyperplasia of Kupffer cells, many of them parasitized by numerous amastigotes (Fig. 10-43).[293] Well-formed granulomas may be seen alongside Kupffer cells with intracellular amastigotes.[292,294] Other patterns include a nodular pattern, with collections of macrophages, lymphocytes, and plasma cells within the lobules and portal tracts harboring few parasites, and a fibrogenic pattern, with perisinusoidal fibrosis that isolates small groups of liver cells with regenerative changes.[293] The differential diagnosis includes *H. capsulatum, P. marneffei,* and *Toxoplasma gondii.*[291] Fibrin ring granulomas have been reported.[227] The diagnosis depends on demonstration of the organism in tissue, typically bone marrow smears or spleen aspirates.[292] In liver tissue, demonstra-

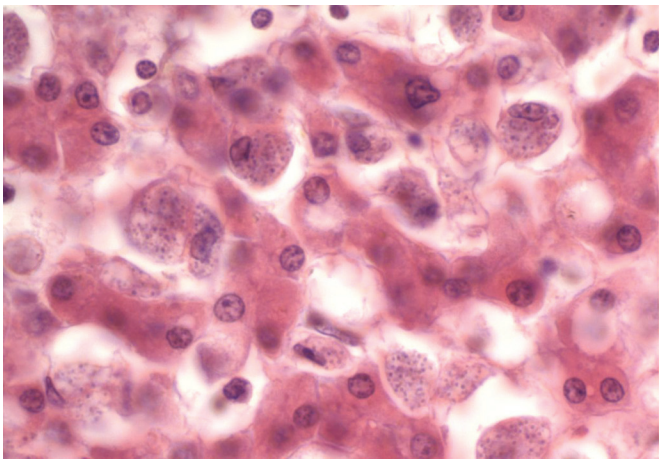

Figure 10-43. Visceral leishmaniasis (kala-azar) in the liver. In the sinusoids, Kupffer cells are filled with amastigotes.

tion of the parasites is best done with Giemsa staining, preferably of touch preparations on glass slides.[289] The presence of a kinetoplast on Giemsa stain is characteristic of *Leishmania* and distinguishes this parasite from *Histoplasma*.[289] Serologic assays are available.

Toxoplasmosis

Toxoplasma gondii is an obligate intracellular parasite usually acquired from ingestion of undercooked pork or lamb, or transplacentally. Cats are a major reservoir. Disseminated infection occurs in bone marrow and solid organ transplant recipients and in AIDS patients. Hepatitis has been reported in apparently healthy persons during acute infection; these patients present with jaundice, rash, and elevated levels of transaminases and alkaline phosphatase.[295,296]

Histologically, *Toxoplasma* hepatitis is characterized as a diffuse hepatitis with infiltration of portal tracts and sinusoids by mononuclear cells associated with focal hepatic necrosis, similar to EBV or CMV hepatitis.[295] Granulomatous hepatitis has also been described.[296] In some cases, *Toxoplasma* cysts have been identified in histiocytes and granulomas.[297] Free tachyzoites have been described within degenerating or necrotic hepatocytes, although they can be difficult to distinguish from detritus.[296] Giemsa stain or immunofluorescent stains may assist in the detection of organisms in tissue. Serologic assay for IgM antibodies to *T. gondii* can be used to establish the diagnosis.

Cryptosporidiosis

Cryptosporidium is a protozoan that causes an opportunistic infection of the gastrointestinal tract resulting in diarrhea. In patients with AIDS, the organism has been known to infect the biliary tree, producing a syndrome similar to primary sclerosing cholangitis.[96] Signs and symptoms include right upper quadrant abdominal pain, nausea, vomiting, fever, and biochemical evidence of anicteric cholestasis.[96] Dilatation of the common bile duct is often seen on ultrasonography or computed tomography scanning, and cholangiography reveals attenuation and pruning of duct branches, stricturing and beading of the proximal intrahepatic bile ducts, and dilatation or stricturing of the extrahepatic duct.[96] The histologic picture reflects the intense periductal inflammatory response elicited by the organism, with portal edema, inflammation, and hyperplastic periductal glands. The biliary epithelium may be reactive or frankly necrotic. Organisms can be detected on the luminal surface of the epithelial lining of small biliary radicles, peribiliary glands, the pancreatic duct, and the gallbladder.[96] Concomitant CMV infection may be found.

REFERENCES

1. Martin A, Lemon SM: Hepatitis A virus: From discovery to vaccines. Hepatology 2006;43:S164-S172.
2. Leach CT: Hepatitis A in the United States. Pediatr Infect Dis J 2004;23:551-552.
3. Skoog SM, Rivard RE, Batts KP, et al: Autoimmune hepatitis preceded by acute hepatitis A infection. Am J Gastroenterol 2002; 97:1568-1569.
4. Huppertz HI, Treichel U, Gassel AM, et al: Autoimmune hepatitis following hepatitis A virus infection. J Hepatol 1995;23:204-208.
5. Hilzenrat N, Zilberman D, Klein T, et al: Autoimmune hepatitis in a genetically susceptible patient: Is it triggered by acute viral hepatitis A? Dig Dis Sci 1999;44:1950-1952.
6. Vento S, Garofano T, Di Perri G, et al: Identification of hepatitis A virus as a trigger for autoimmune chronic hepatitis type 1 in susceptible individuals. Lancet 1991;337:1183-1187.
7. Goldin RD: Viral hepatitis. Curr Diagn Pathol 1994;1:70-76.
8. Ruel M, Sevestre H, Henry-Biabaud E, et al: Fibrin ring granulomas in hepatitis A. Dig Dis Sci 1992;37:1915-1917.
9. Ponz E, Garcia-Pagan JC, Bruguera M, et al: Hepatic fibrin-ring granulomas in a patient with hepatitis A. Gastroenterology 1991;100:268-270.
10. Pungpapong S, Kim WR, Poterucha JJ: Natural history of hepatitis B virus infection: An update for clinicians. Mayo Clin Proc 2007;82:967-975.
11. Lai CL, Ratziu V, Yuen MF, et al: Viral hepatitis B. Lancet 2003;362:2089-2094.
12. Hunt CM, McGill JM, Allen MI, et al: Clinical relevance of hepatitis B viral mutations. Hepatology 2000;31:1037-1044.
13. Akuta N, Kumada H: Influence of hepatitis B virus genotypes on the response to antiviral therapies. J Antimicrob Chemother 2005;55:139-142.
14. Trepo C, Guillevin L: Polyarteritis nodosa and extrahepatic manifestations of HBV infection: The case against autoimmune intervention in pathogenesis. J Autoimmun 2001;16:269-274.
15. Fattovich G, Bortolotti F, Donato F: Natural history of chronic hepatitis B: Special emphasis on disease progression and prognostic factors. J Hepatol 2008;48:335-352.
16. Hsu YS, Chien RN, Yeh CT, et al: Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. Hepatology 2002;35:1522-1527.
17. Ishak KG: Chronic hepatitis: Morphology and nomenclature. Mod Pathol 1994;7:690-713.
18. Naoumov NV, Portmann BC, Tedder RS, et al: Detection of hepatitis B virus antigens in liver tissue: A relation to viral replication and histology in chronic hepatitis B infection. Gastroenterology 1990;99:1248-1253.
19. Hsu HC, Lai MY, Su IJ, et al: Correlation of hepatocyte HBsAg expression with virus replication and liver pathology. Hepatology 1988;8:749-754.
20. Thomson EC, Main J: Advances in hepatitis B and C. Curr Opin Infect Dis 2004;17:449-459.

21. Walker N, Apel R, Kerlin P, et al: Hepatitis B virus infection in liver allografts. Am J Surg Pathol 1993;17:666-677.
22. Harrison RF, Davies MH, Goldin RD, et al: Recurrent hepatitis B in liver allografts: A distinctive form of rapidly developing cirrhosis. Histopathology 1993;23:21-28.
23. Davies SE, Portmann BC, O'Grady JG, et al: Hepatic histological findings after transplantation for chronic hepatitis B virus infection, including a unique pattern of fibrosing cholestatic hepatitis. Hepatology 1991;13:150-157.
24. Benner KG, Lee RG, Keeffe EB, et al: Fibrosing cytolytic liver failure secondary to recurrent hepatitis B after liver transplantation. Gastroenterology 1992;103:1307-1312.
25. Fang JW, Wright TL, Lau JY: Fibrosing cholestatic hepatitis in patient with HIV and hepatitis B. Lancet 1993;342:1175.
26. McIvor C, Morton J, Bryant A, et al: Fatal reactivation of precore mutant hepatitis B virus associated with fibrosing cholestatic hepatitis after bone marrow transplantation. Ann Intern Med 1994;121:274-275.
27. Sulkowski MS: Viral hepatitis and HIV coinfection. J Hepatol 2008;48:353-367.
28. Thimme R, Spangenberg HC, Blum HE: Hepatitis B or hepatitis C and human immunodeficiency virus infection. J Hepatol 2005;42(Suppl):S37-S44.
29. Wong T, Lee SS: Hepatitis C: A review for primary care physicians. CMAJ Can Med Assoc J 2006;174:649-659.
30. Giannini C, Brechot C: Hepatitis C virus biology. Cell Death Differ 2003;10(Suppl 1):S27-S38.
31. Orland JR, Wright TL, Cooper S: Acute hepatitis C. Hepatology 2001;33:321-327.
32. Zein NN: Clinical significance of hepatitis C virus genotypes. Clin Microbiol Rev 2000;13:223-235.
33. Mondelli MU, Silini E: Clinical significance of hepatitis C virus genotypes. J Hepatol 1999;31(Suppl 1):65-70.
34. Hatzakis A, Katsoulidou A, Kaklamani E, et al: Hepatitis C virus 1b is the dominant genotype in HCV-related carcinogenesis: A case-control study. Int J Cancer 1996;68:51-53.
35. Marcellin P: Hepatitis C: The clinical spectrum of the disease. J Hepatol 1999;31(Suppl 1):9-16.
36. Mondelli MU, Cerino A, Cividini A: Acute hepatitis C: Diagnosis and management. J Hepatol 2005;42(Suppl):S108-S114.
37. Chung RT: Acute hepatitis C virus infection. Clin Infect Dis 2005;41(Suppl 1):S14-S17.
38. Caruntu FA, Benea L: Acute hepatitis C virus infection: Diagnosis, pathogenesis, treatment. J Gastrointestin Liver Dis 2006;15:249-256.
39. Gerlach JT, Diepolder HM, Zachoval R, et al: Acute hepatitis C: High rate of both spontaneous and treatment-induced viral clearance. Gastroenterology 2003;125:80-88.
40. Obermayer-Straub P, Manns MP: Hepatitis C and D, retroviruses and autoimmune manifestations. J Autoimmun 2001;16:275-285.
41. Cassani F, Cataleta M, Valentini P, et al: Serum autoantibodies in chronic hepatitis C: Comparison with autoimmune hepatitis and impact on the disease profile. Hepatology 1997;26:561-566.
42. Scheuer PJ, Ashrafzadeh P, Sherlock S, et al: The pathology of hepatitis C. Hepatology 1992;15:567-571.
43. Negro F: Hepatitis C virus and liver steatosis: When fat is not beautiful. J Hepatol 2004;40:533-535.
44. Castera L, Chouteau P, Hezode C, et al: Hepatitis C virus-induced hepatocellular steatosis. Am J Gastroenterol 2005;100:711-715.
45. Gaya DR, Thorburn D, Oien KA, et al: Hepatic granulomas: A 10 year single centre experience. J Clin Pathol 2003;56:850-853.
46. Emile JF, Sebagh M, Feray C, et al: The presence of epithelioid granulomas in hepatitis C virus-related cirrhosis. Hum Pathol 1993;24:1095-1097.
47. Goldin RD, Levine TS, Foster GR, et al: Granulomas and hepatitis C. Histopathology 1996;28:265-257.
48. Harada K, Minato H, Hiramatsu K, et al: Epithelioid cell granulomas in chronic hepatitis C: Immunohistochemical character and histological marker of favourable response to interferon-alpha therapy. Histopathology 1998;33:216-221.
49. Veerabagu MP, Finkelstein SD, Rabinovitz M: Granulomatous hepatitis in a patient with chronic hepatitis C treated with interferon-alpha. Dig Dis Sci 1997;42:1445-1448.
50. Propst A, Propst T, Dietze O, et al: Development of granulomatous hepatitis during treatment with interferon-alpha 2b. Dig Dis Sci 1995;40:2117-2118.
51. Mert A, Tabak F, Ozaras R, et al: Hepatic granulomas in chronic hepatitis C. J Clin Gastroenterol 2001;33:342-343.
52. Greenson JK, Svoboda-Newman SM, Merion RM, et al: Histologic progression of recurrent hepatitis C in liver transplant allografts. Am J Surg Pathol 1996;20:731-738.
53. Schluger LK, Sheiner PA, Thung SN, et al: Severe recurrent cholestatic hepatitis C following orthotopic liver transplantation. Hepatology 1996;23:971-976.
54. Rosenberg PM, Farrell JJ, Abraczinskas DR, et al: Rapidly progressive fibrosing cholestatic hepatitis: Hepatitis C virus in HIV coinfection. Am J Gastroenterol 2002;97:478-483.
55. Lim HL, Lau GK, Davis GL, et al: Cholestatic hepatitis leading to hepatic failure in a patient with organ-transmitted hepatitis C virus infection. Gastroenterology 1994;106:248-251.
56. Zylberberg H, Carnot F, Mamzer MF, et al: Hepatitis C virus-related fibrosing cholestatic hepatitis after renal transplantation. Transplantation 1997;63:158-160.
57. Toth CM, Pascual M, Chung RT, et al: Hepatitis C virus-associated fibrosing cholestatic hepatitis after renal transplantation: Response to interferon-alpha therapy. Transplantation 1998;66:1254-1258.
58. Makris M, Preston FE, Rosendaal FR, et al: The natural history of chronic hepatitis C in haemophiliacs. Br J Haematol 1996;94:746-752.
59. Hanley JP, Jarvis LM, Andrews J, et al: Investigation of chronic hepatitis C infection in individuals with haemophilia: Assessment of invasive and non-invasive methods. Br J Haematol 1996;94:159-165.
60. McFarlane BM, Bridger CB, Smith HM, et al: Autoimmune mechanisms in chronic hepatitis B and delta virus infections. Eur J Gastroenterol Hepatol 1995;7:615-621.
61. Emerson SU, Purcell RH: Hepatitis E. Pediatr Infect Dis J 2007;26:1147-1148.
62. Wang L, Zhuang H: Hepatitis E: An overview and recent advances in vaccine research. World J Gastroenterol 2004;10:2157-2162.
63. Vento S, Guella L, Mirandola F, et al: Epstein-Barr virus as a trigger for autoimmune hepatitis in susceptible individuals. Lancet 1995;346:608-609.
64. Kimura H, Nagasaka T, Hoshino Y, et al: Severe hepatitis caused by Epstein-Barr virus without infection of hepatocytes. Hum Pathol 2001;32:757-762.
65. Sanchez F, Gimeno-Bayon JL, Esgueva R, et al: Fatal liver failure: Molecular evidence for chronic active Epstein-Barr virus infection. Ann Diagn Pathol 2008;12:368-371.
66. White NJ, Juel-Jensen BE: Infectious mononucleosis hepatitis. Semin Liver Dis 1984;4:301-306.
67. Feranchak AP, Tyson RW, Narkewicz MR, et al: Fulminant Epstein-Barr viral hepatitis: Orthotopic liver transplantation and review of the literature. Liver Transpl Surg 1998;4:469-476.
68. Alshak NS, Jiminez AM, Gedebou M, et al: Epstein-Barr virus infection in liver transplantation patients: Correlation of histopathology and semiquantitative Epstein-Barr virus-DNA recovery using polymerase chain reaction. Hum Pathol 1993;24:1306-1312.
69. Biest S, Schubert TT: Chronic Epstein-Barr virus infection: A cause of granulomatous hepatitis? J Clin Gastroenterol 1989;11:343-346.
70. Nenert M, Mavier P, Dubuc N, et al: Epstein-Barr virus infection and hepatic fibrin-ring granulomas. Hum Pathol 1988;19:608-610.

71. Suh N, Liapis H, Misdraji J, et al: Epstein-Barr virus hepatitis: Diagnostic value of in situ hybridization, polymerase chain reaction, and immunohistochemistry on liver biopsy from immunocompetent patients. Am J Surg Pathol 2007;31:1403-1409.
72. Washington K: Update on post-liver transplantation infections, malignancies, and surgical complications. Adv Anat Pathol 2005;12:221-226.
73. Bonkowsky HL, Lee RV, Klatskin G: Acute granulomatous hepatitis: Occurrence in cytomegalovirus mononucleosis. JAMA 1975;233:1284-1288.
74. Clarke J, Craig RM, Saffro R, et al: Cytomegalovirus granulomatous hepatitis. Am J Med 1979;66:264-269.
75. Lobdell DH: "Ring" granulomas in cytomegalovirus hepatitis. Arch Pathol Lab Med 1987;111:881-882.
76. Goodman ZD, Ishak KG, Sesterhenn IA: Herpes simplex hepatitis in apparently immunocompetent adults. Am J Clin Pathol 1986;85:694-699.
77. Krilov LR, Rubin LG, Frogel M, et al: Disseminated adenovirus infection with hepatic necrosis in patients with human immunodeficiency virus infection and other immunodeficiency states. Rev Infect Dis 1990;12:303-307.
78. Janner D, Petru AM, Belchis D, et al: Fatal adenovirus infection in a child with acquired immunodeficiency syndrome. Pediatr Infect Dis J 1990;9:434-436.
79. Sokal EM, Melchior M, Cornu C, et al: Acute parvovirus B19 infection associated with fulminant hepatitis of favourable prognosis in young children. Lancet 1998;352:1739-1741.
80. Langnas AN, Markin RS, Cattral MS, et al: Parvovirus B19 as a possible causative agent of fulminant liver failure and associated aplastic anemia. Hepatology 1995;22:1661-1665.
81. Yoto Y, Kudoh T, Haseyama K, et al: Human parvovirus B19 infection associated with acute hepatitis. Lancet 1996;347:868-869.
82. Lee WM, Brown KE, Young NS, et al: Brief report: No evidence for parvovirus B19 or hepatitis E virus as a cause of acute liver failure. Dig Dis Sci 2006;51:1712-1715.
83. Wong S, Young NS, Brown KE: Prevalence of parvovirus B19 in liver tissue: No association with fulminant hepatitis or hepatitis-associated aplastic anemia. J Infect Dis 2003;187:1581-1586.
84. Tameda Y, Kosaka Y, Shiraki K, et al: Hepatitis in an adult with rubella. Intern Med 1993;32:580-583.
85. Onji M, Kumon I, Kanaoka M, et al: Intrahepatic lymphocyte subpopulations in acute hepatitis in an adult with rubella. Am J Gastroenterol 1988;83:320-322.
86. McLellan RK, Gleiner JA: Acute hepatitis in an adult with rubeola. JAMA 1982;247:2000-2001.
87. Cheeseman SH, Cleveland RH, Mark EJ: Case records of the Massachusetts General Hospital: Weekly clinicopathological exercises. Case 34-1988: Progressive pulmonary consolidations in a 10-year-old boy with Evans' syndrome. N Engl J Med 1988;319:495-509.
88. Chau TN, Lee KC, Yao H, et al: SARS-associated viral hepatitis caused by a novel coronavirus: Report of three cases. Hepatology 2004;39:302-310.
89. Boag FC, Dean R, Hawkins DA, et al: Abnormalities of liver function during HIV seroconversion illness. Int J STD AIDS 1992;3:46-48.
90. Molina JM, Welker Y, Ferchal F, et al: Hepatitis associated with primary HIV infection. Gastroenterology 1992;102:739.
91. Steeper TA, Rosenstein H, Weiser J, et al: Bacillary epithelioid angiomatosis involving the liver, spleen, and skin in an AIDS patient with concurrent Kaposi's sarcoma. Am J Clin Pathol 1992;97:713-718.
92. Perkocha LA, Geaghan SM, Yen TS, et al: Clinical and pathological features of bacillary peliosis hepatis in association with human immunodeficiency virus infection. N Engl J Med 1990;323:1581-1586.
93. Jagadha V, Andavolu RH, Huang CT: Granulomatous inflammation in the acquired immune deficiency syndrome. Am J Clin Pathol 1985;84:598-602.
94. Terada S, Reddy KR, Jeffers LJ, et al: Microsporidan hepatitis in the acquired immunodeficiency syndrome. Ann Intern Med 1987;107:61-62.
95. Beaugerie L, Teilhac MF, Deluol AM, et al: Cholangiopathy associated with *Microsporidia* infection of the common bile duct mucosa in a patient with HIV infection. Ann Intern Med 1992;117:401-402.
96. Teixidor HS, Godwin TA, Ramirez EA: Cryptosporidiosis of the biliary tract in AIDS. Radiology 1991;180:51-56.
97. Pol S, Romana CA, Richard S, et al: *Microsporidia* infection in patients with the human immunodeficiency virus and unexplained cholangitis. N Engl J Med 1993;328:95-99.
98. Cello JP: Acquired immunodeficiency syndrome cholangiopathy: Spectrum of disease. Am J Med 1989;86:539-546.
99. Forbes A, Blanshard C, Gazzard B: Natural history of AIDS related sclerosing cholangitis: A study of 20 cases. Gut 1993;34:116-121.
100. Hasan FA, Jeffers LJ, Welsh SW, et al: Hepatic involvement as the primary manifestation of Kaposi's sarcoma in the acquired immune deficiency syndrome, Am J Gastroenterol 1989;84:1449-1451.
101. O'Leary JG, Zachary K, Misdraji J, et al: De novo autoimmune hepatitis during immune reconstitution in an HIV-infected patient receiving highly active antiretroviral therapy. Clin Infect Dis 2008;46:e12-e14.
102. Howard CR, Ellis DS, Simpson DI: Exotic viruses and the liver. Semin Liver Dis 1984;4:361-374.
103. Quaresma JA, Duarte MI, Vasconcelos PF: Midzonal lesions in yellow fever: A specific pattern of liver injury caused by direct virus action and in situ inflammatory response. Med Hypotheses 2006;67:618-621.
104. Francis TI, Moore DL, Edington GM, et al: A clinicopathological study of human yellow fever. Bull World Health Organ 1972;46:659-667.
105. Monath TP, Barrett AD: Pathogenesis and pathophysiology of yellow fever. Adv Virus Res 2003;60:343-395.
106. Ishak KG, Walker DH, Coetzer JA, et al: Viral hemorrhagic fevers with hepatic involvement: Pathologic aspects with clinical correlations. Prog Liver Dis 1982;7:495-515.
107. Malavige GN, Fernando S, Fernando DJ, et al: Dengue viral infections. Postgrad Med J 2004;80:588-601.
108. de Macedo FC, Nicol AF, Cooper LD, et al: Histologic, viral, and molecular correlates of dengue fever infection of the liver using highly sensitive immunohistochemistry. Diagn Mol Pathol 2006;15:223-228.
109. Huerre MR, Lan NT, Marianneau P, et al: Liver histopathology and biological correlates in five cases of fatal dengue fever in Vietnamese children. Virchows Archiv 2001;438:107-115.
110. Walker DH, McCormick JB, Johnson KM, et al: Pathologic and virologic study of fatal Lassa fever in man. Am J Pathol 1982;107:349-356.
111. Alvarez SZ: Hepatobiliary tuberculosis. J Gastroenterol Hepatol 1998;13:833-839.
112. Chong VH: Hepatobiliary tuberculosis: A review of presentations and outcomes. South Med J 2008;101:356-361.
113. Huang WT, Wang CC, Chen WJ, et al: The nodular form of hepatic tuberculosis: A review with five additional new cases. J Clin Pathol 2003;56:835-839.
114. Essop AR, Posen JA, Hodkinson JH, et al: Tuberculosis hepatitis: A clinical review of 96 cases. Q J Med 1984;53:465-477.
115. Harrington PT, Gutierrez JJ, Ramirez-Ronda CH, et al: Granulomatous hepatitis. Rev Infect Dis 1982;4:638-655.
116. Maharaj B, Leary WP, Pudifin DJ: A prospective study of hepatic tuberculosis in 41 black patients. Q J Med 1987;63:517-522.

117. Wang JY, Hsueh PR, Wang SK, et al: Disseminated tuberculosis: A 10-year experience in a medical center. Medicine (Baltimore) 2007;86:39-46.
118. Maglinte DD, Alvarez SZ, Ng AC, et al: Patterns of calcifications and cholangiographic findings in hepatobiliary tuberculosis. Gastrointest Radiol 1988;13:331-335.
119. Alcantara-Payawal DE, Matsumura M, Shiratori Y, et al: Direct detection of *Mycobacterium tuberculosis* using polymerase chain reaction assay among patients with hepatic granuloma. J Hepatol 1997;27:620-627.
120. Diaz ML, Herrera T, Lopez-Vidal Y, et al: Polymerase chain reaction for the detection of *Mycobacterium tuberculosis* DNA in tissue and assessment of its utility in the diagnosis of hepatic granulomas. J Lab Clin Med 1996;127:359-363.
121. Orenstein MS, Tavitian A, Yonk B, et al: Granulomatous involvement of the liver in patients with AIDS. Gut 1985;26:1220-1225.
122. Hickey N, McNulty JG, Osborne H, et al: Acute hepatobiliary tuberculosis: A report of two cases and a review of the literature. Eur Radiol 1999;9:886-889.
123. Kahn SA, Saltzman BR, Klein RS, et al: Hepatic disorders in the acquired immune deficiency syndrome: A clinical and pathological study. Am J Gastroenterol 1986;81:1145-1148.
124. Farhi DC, Mason UG 3rd, Horsburgh CR Jr: Pathologic findings in disseminated *Mycobacterium avium-intracellulare* infection: A report of 11 cases. Am J Clin Pathol 1986;85:67-72.
125. Chen TS, Drutz DJ, Whelan GE: Hepatic granulomas in leprosy: Their relation to bacteremia. Arch Pathol Lab Med 1976;100:182-185.
126. Ferrari TC, Araujo MG, Ribeiro MM: Hepatic involvement in lepromatous leprosy. Lepr Rev 2002;73:72-75.
127. Bodurtha A, Kim YH, Laucius JF, et al: Hepatic granulomas and other hepatic lesions associated with BCG immunotherapy for cancer. Am J Clin Pathol 1974;61:747-752.
128. Hunt JS, Silverstein MJ, Sparks FC, et al: Granulomatous hepatitis: A complication of B.C.G. immunotherapy. Lancet 1973;2:820-821.
129. Lamm DL, van der Meijden PM, Morales A, et al: Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. J Urol 1992;147:596-600.
130. Barza MJ, Blum JH, Graeme-Cook FM: Case records of the Massachusetts General Hospital: Weekly clinicopathological exercises. Case 29-1998: A 57-year-old man with fever and jaundice after intravesical instillation of bacille Calmette-Guerin for bladder cancer. N Engl J Med 1998;339:831-837.
131. Schattner A, Gilad A, Cohen J: Systemic granulomatosis and hypercalcaemia following intravesical bacillus Calmette-Guerin immunotherapy. J Intern Med 2002;251:272-277.
132. Proctor DD, Chopra S, Rubenstein SC, et al: Mycobacteremia and granulomatous hepatitis following initial intravesical bacillus Calmette-Guerin instillation for bladder carcinoma. Am J Gastroenterol 1993;88:1112-1115.
133. Leebeek FW, Ouwendijk RJ, Kolk AH, et al: Granulomatous hepatitis caused by bacillus Calmette-Guerin (BCG) infection after BCG bladder instillation. Gut 1996;38:616-618.
134. Saint-Marc Girardin MF, Zafrani ES, Chaumette MT, et al: Hepatic granulomas in Whipple's disease. Gastroenterology 1984;86:753-756.
135. Chateil JF, Brun M, Perel Y, et al: Granulomatous hepatitis in *Pasteurella multocida* infection. Eur Radiol 1998;8:588-591.
136. Stjernberg U, Silseth C, Ritland S: Granulomatous hepatitis in *Yersinia enterocolitica* infection. Hepatogastroenterology 1987;34:56-57.
137. Muorah M, Hinds R, Verma A, et al: Liver abscesses in children: A single center experience in the developed world. J Pediatr Gastroenterol Nutr 2006;42:201-206.
138. Rahimian J, Wilson T, Oram V, et al: Pyogenic liver abscess: Recent trends in etiology and mortality. Clin Infect Dis 2004;39:1654-1659.
139. Ruiz-Hernandez JJ, Leon-Mazorra M, Conde-Martel A, et al: Pyogenic liver abscesses: Mortality-related factors. Eur J Gastroeinterol Hepatol 2007;19:853-858.
140. Chan KS, Yu WL, Tsai CL, et al: Pyogenic liver abscess caused by *Klebsiella pneumoniae*: Analysis of the clinical characteristics and outcomes of 84 patients. Chin Med J (Engl) 2007;120:136-139.
141. Thomsen RW, Jepsen P, Sorensen HT: Diabetes mellitus and pyogenic liver abscess: Risk and prognosis. Clin Infect Dis 2007;44:1194-1201.
142. Chen W, Chen CH, Chiu KL, et al: Clinical outcome and prognostic factors of patients with pyogenic liver abscess requiring intensive care. Crit Care Med 2008;36:1184-1188.
143. Chong VH, Yong AM, Wahab AY: Gas-forming pyogenic liver abscess. Singapore Med J 2008;49:e123-e125.
144. Vadillo M, Corbella X, Pac V, et al: Multiple liver abscesses due to *Yersinia enterocolitica* discloses primary hemochromatosis: Three cases reports and review. Clin Infect Dis 1994;18:938-941.
145. Farrer W, Kloser P, Ketyer S: *Yersinia pseudotuberculosis* sepsis presenting as multiple liver abscesses. Am J Med Sci 1988;295:129-132.
146. Santoro MJ, Chen YK, Seid NS, et al: *Yersinia enterocolitica* liver abscesses unmasking idiopathic hemochromatosis. J Clin Gastroenterol 1994;18:253-254.
147. Bergmann TK, Vinding K, Hey H: Multiple hepatic abscesses due to *Yersinia enterocolitica* infection secondary to primary haemochromatosis. Scand J Gastroenterol 2001;36:891-895.
148. Sabbaj J: Anaerobes in liver abscess. Rev Infect Dis 1984;6(Suppl 1):S152-S156.
149. Brook I, Fraizer EH: Role of anaerobic bacteria in liver abscesses in children. Pediatr Infect Dis J 1993;12:743-747.
150. Kazmi KA, Rab SM: Primary hepatic actinomycosis: A diagnostic problem. Am J Trop Med Hygiene 1980;40:310-311.
151. Christodoulou N, Papadakis I, Velegrakis M: Actinomycotic liver abscess: Case report and review of the literature. Chir Ital 2004;56:141-146.
152. Hilfiker ML: Disseminated actinomycosis presenting as a renal tumor with metastases. J Pediatr Surg 2001;36:1577-1578.
153. Sharma M, Briski LE, Khatib R: Hepatic actinomycosis: An overview of salient features and outcome of therapy. Scand J Infect Dis 2002;34:386-391.
154. Lamps LW, Havens JM, Sjostedt A, et al: Histologic and molecular diagnosis of tularemia: A potential bioterrorism agent endemic to North America. Mod Pathol 2004;17:489-495.
155. Apisarnthanarak A, Apisarnthanarak P, Mundy LM: Computed tomography characteristics of *Burkholderia pseudomallei* liver abscess. Clin Infect Dis 2006;42:989-993.
156. White NJ: Melioidosis. Lancet 2003;361:1715-1722.
157. Braun TI, Travis D, Dee RR, et al: Liver abscess due to *Listeria monocytogenes*: Case report and review. Clin Infect Dis 1993;17:267-269.
158. Rieder J, Lechner M, Lass-Floerl C, et al: Successful management of *Aspergillus* liver abscess in a patient with necrotizing fasciitis. Dig Dis Sci 2007;52:1548-1553.
159. Fang CT, Lai SY, Yi WC, et al: *Klebsiella pneumoniae* genotype K1: An emerging pathogen that causes septic ocular or central nervous system complications from pyogenic liver abscess. Clin Infect Dis 2007;45:284-292007.
160. Tan YM, Chee SP, Soo KC, et al: Ocular manifestations and complications of pyogenic liver abscess. World J Surg 2004;28:38-42.
161. Sinanan MN: Acute cholangitis. Infect Dis Clin North Am 1992;6:571-599.
162. Charcot JM: Leçons Sur Les Maladies du Foi des Voies Fliares et des Rins. Paris, Faculté de Médicine de Paris, 1877.

163. Reynolds BM, Dargan EL: Acute obstructive cholangitis: A distinct clinical syndrome. Ann Surg 1959;150:299-303.
164. O'Connor MJ, Schwartz ML, McQuarrie DG, et al: Acute bacterial cholangitis: An analysis of clinical manifestation. Arch Surg 1982;117:437-441.
165. Mukaiya M, Hirata K, Katsuramaki T, et al: Isolated bacteria and susceptibilities to antimicrobial agents in biliary infections. Hepatogastroenterology 2005;52:686-690.
166. Qureshi WA: Approach to the patient who has suspected acute bacterial cholangitis. Gastroenterol Clin North Am 2006;35:409-423.
167. Carpenter HA: Bacterial and parasitic cholangitis. Mayo Clin Proc 1998;73:473-478.
168. Shimada H, Nihmoto S, Matsuba A, et al: Acute cholangitis: A histopathologic study. J Clin Gastroenterol 1988;10:197-200.
169. Lim JH: Oriental cholangiohepatitis: Pathologic, clinical, and radiologic features. AJR Am J Roentgenol 1991;157:1-8.
170. Chung RT, Varghese JC, Sheffer EC: Case records of the Massachusetts General Hospital: Weekly clinicopathological exercises. Case 28-2001: A 44-year-old woman with chills, fever, jaundice, and hepatic abscesses. N Engl J Med 2001;345:817-823.
171. Williams RK, Crossley K: Acute and chronic hepatic involvement of brucellosis. Gastroenterology 1982;83:455-458.
172. Hunt AC, Bothwell PW: Histological findings in human brucellosis. J Clin Pathol 1967;20:267-272.
173. Spink WW, Hoffbauer FW: Histopathology of the liver in human brucellosis. J Lab Clin Med 1949;34:40-58.
174. Akritidis N, Tzivras M, Delladetsima I, et al: The liver in brucellosis. Clinical Gastroenterol Hepatol 2007;5:1109-1112.
175. Jordans HG, DeBruin KD: Granulomas in *Brucella melitensis* infection. Ann Intern Med 1980;92:264-265.
176. Ledro D, Llamas R, Herrerias JM, et al: The presence of granulomas due to *Brucella melitensis* in hepatitis. J Infect Dis 1983;147:606-607.
177. Bruguera M, Cervantes F: Hepatic granulomas in brucellosis. Ann Intern Med 1980;92:571-572.
178. Fernandez Guerrero ML, Diaz Curiel M, Cortes Cansino JM: Hepatic granulomas in brucellosis. Ann Intern Med 1980;92: 572.
179. Young EJ: *Brucella melitensis* hepatitis: The absence of granulomas. Ann Intern Med 1979;91:414-415.
180. Villar JM, Garrote D, Villegas MT, et al: Hepatic brucelloma. J Am Coll Surg 2002;194:86.
181. Ariza J, Pigrau C, Canas C, et al: Current understanding and management of chronic hepatosplenic suppurative brucellosis. Clin Infect Dis 2001;32:1024-1033.
182. Arisoy ES, Correa AG, Wagner ML, et al: Hepatosplenic cat-scratch disease in children: Selected clinical features and treatment. Clin Infect Dis 1999;28:778-784.
183. Lamps LW, Gray GF, Scott MA: The histologic spectrum of hepatic cat scratch disease: A series of six cases with confirmed *Bartonella henselae* infection. Am J Surg Pathol 1996;20:1253-1259.
184. Lenoir AA, Storch GA, DeSchryver-Kecskemeti K, et al: Granulomatous hepatitis associated with cat scratch disease. Lancet 1988;1:1132-1136.
185. Ventura A, Massei F, Not T, et al: Systemic *Bartonella henselae* infection with hepatosplenic involvement. J Pediatric Gastroenterol Nutr 1999;29:52-56.
186. Malatack JJ, Jaffe R: Granulomatous hepatitis in three children due to cat-scratch disease without peripheral adenopathy: An unrecognized cause of fever of unknown origin. Am J Dis Child 1993;147:949-953.
187. Liston TE, Koehler JE: Granulomatous hepatitis and necrotizing splenitis due to *Bartonella henselae* in a patient with cancer: Case report and review of hepatosplenic manifestations of bartonella infection. Clin Infect Dis 1996;22:951-957.
188. Connor BA, Schwartz E: Typhoid and paratyphoid fever in travellers. Lancet Infect Dis 2005;5:623-628.
189. Parry CM, Hien TT, Dougan G, et al: Typhoid fever. N Engl J Med 2002;347:1770-1782.
190. Rubin EJ, Graeme-Cook FM: Case records of the Massachusetts General Hospital: Weekly clinicopathological exercises. Case 22-2001: A 25-year-old woman with fever and abnormal liver function. N Engl J Med 2001;345:201-205.
191. Sorabjee JS: The liver in enteric fever and leptospirosis. Indian J Gastroenterol 2001;20(Suppl 1):C44-C46.
192. Pais P: A hepatitis like picture in typhoid fever. Br Med J Clin Res Ed 1984;289:225-226.
193. Zaidi SA, Singer C: Gastrointestinal and hepatic manifestations of tickborne diseases in the United States. Clin Infect Dis 2002;34:1206-1212.
194. Lamps LW: Hepatic granulomas, with an emphasis on infectious causes. Adv Anat Pathol 2008;15:309-318.
195. Currie BJ: Melioidosis: An important cause of pneumonia in residents of and travellers returned from endemic regions. Eur Respir J 2003;22:542-550.
196. Piggott JA, Hochholzer L: Human melioidosis: A histopathologic study of acute and chronic melioidosis. Arch Pathol Lab Med 1970;90:101-111.
197. Scholing M, Schneeberger PM, van den Dries P, et al: Clinical features of liver involvement in adult patients with listeriosis: Review of the literature. Infection 2007;35:212-218.
198. De Vega T, Echevarria S, Crespo J, et al: Acute hepatitis by *Listeria monocytogenes* in an HIV patient with chronic HBV hepatitis. J Clin Gastroenterol 1992;15:251-255.
199. Keisler DS Jr, Starke W, Looney DJ, et al: Early syphilis with liver involvement. JAMA 1982;247:1999-2000.
200. Campisi D, Whitcomb C: Liver disease in early syphilis. Arch Intern Med 1979;139:365-366.
201. Baker AL, Kaplan MM, Wolfe HJ, et al: Liver disease associated with early syphilis. N Engl J Med 1971;284:1422-1423.
202. Ridruejo E, Mordoh A, Herrera F, et al: Severe cholestatic hepatitis as the first symptom of secondary syphilis. Dig Dis Sci 2004;49:1401-1404.
203. Ozaki T, Takemoto K, Hosono H, et al: Secondary syphilitic hepatitis in a fourteen-year-old male youth. Pediatr Infect Dis J 2002;21:439-441.
204. Mullick CJ, Liappis AP, Benator DA, et al: Syphilitic hepatitis in HIV-infected patients: A report of 7 cases and review of the literature. Clin Infect Dis 2004;39:e100-e105.
205. Greenstone CL, Saint S, Moseley RH: Clinical problem solving: A hand-carried diagnosis. N Engl J Med 2007;356:2407-2411.
206. Pareek SS: Liver involvement in secondary syphilis. Dig Dis Sci 1979;24:41-43.
207. Sobel HJ, Wolf EH: Liver involvement in early syphilis. Arch Pathol Lab Med 1972;93:565-568.
208. Longstreth P, Hoke AW, Elroy C: Hepatitis and bone destruction as uncommon manifestations of early syphilis: Report of a case. Arch Dermatol 1976;112:1451-1454.
209. Koff RS, Gang DL: Case records of the Massachusetts General Hospital: Weekly clinicopathological exercises. Case 27-1983: A 25 year old man with liver disease. N Engl J Med 1983;309:1127-1128.
210. Maincent G, Labadie H, Fabre M, et al: Tertiary hepatic syphilis: A treatable cause of multinodular liver. Dig Dis Sci 1997;42:447-450.
211. Vainrub B: Bacterial infections of the liver and biliary tract: Laboratory studies to determine etiology. Lab Res Methods Biol Med 1983;7:119-128.
212. de Brito T, Menezes LF, Lima DM, et al: Immunohistochemical and in situ hybridization studies of the liver and kidney in human leptospirosis. Virchows Archiv 2006;448:576-583.

213. de Brito T, Penna DO, Hoshino S, et al: Cholestasis in human leptospirosis: A clinical, histochemical, biochemical and electron microscopy study based on liver biopsies. Beitr Pathol Anat 1970;140:345-361.
214. de Brito T, Machado MM, Montans SD, et al: Liver biopsy in human leptospirosis: A light and electron microscopy study. Virchows Arch Pathol Anat Physiol Klin Med 1967;342:61-69.
215. Goellner MH, Agger WA, Burgess JH, et al: Hepatitis due to recurrent Lyme disease. Ann Intern Med 1988;108:707-708.
216. Zanchi AC, Gingold AR, Theise ND, et al: Necrotizing granulomatous hepatitis as an unusual manifestation of Lyme disease. Dig Dis Sci 2007;52:2629-2632.
217. Srigley JR, Vellend H, Palmer N, et al: Q-fever: The liver and bone marrow pathology. Am J Surg Pathol 1985;9:752-758.
218. Hofmann CE, Heaton JW, Jr.: Q fever hepatitis: Clinical manifestations and pathological findings. Gastroenterology 1982;83:474-479.
219. Modol JM, Llamazares JF, Mate JL, et al: Acute abdominal pain and Q fever. Eur J Clin Microbiol Infect Dis 1999;18:158-160.
220. Travis LB, Travis WD, Li CY, et al: Q fever: A clinicopathologic study of five cases. Arch Pathol Lab Med 1986;110:1017-1020.
221. Qizilbash AH: The pathology of Q fever as seen on liver biopsy. Arch Pathol Lab Med 1983;107:364-367.
222. Silver SS, McLeish WA: "Doughnut" granulomas in Q fever. Can Med Assoc J 1984;130:102-104.
223. Font J, Bruguera M, Perez-Villa F, et al: Hepatic fibrin-ring granulomas caused by *Staphylococcus epidermidis* generalized infection. Gastroenterology 1987;93:1449-1451.
224. Stricker BH, Blok AP, Babany G, et al: Fibrin ring granulomas and allopurinol. Gastroenterology 1989;96:1199-1203.
225. Vanderstigel M, Zafrani ES, Lejonc JL, et al: Allopurinol hypersensitivity syndrome as a cause of hepatic fibrin-ring granulomas. Gastroenterology 1986;90:188-190.
226. Marazuela M, Moreno A, Yebra M, et al: Hepatic fibrin-ring granulomas: A clinicopathologic study of 23 patients. Hum Pathol 1991;22:607-613.
227. Moreno A, Marazuela M, Yebra M, et al: Hepatic fibrin-ring granulomas in visceral leishmaniasis. Gastroenterology 1988;95:1123-1126.
228. de Bayser L, Roblot P, Ramassamy A, et al: Hepatic fibrin-ring granulomas in giant cell arteritis. Gastroenterology 1993;105:272-273.
229. Voigt JJ, Delsol G, Fabre J: Liver and bone marrow granulomas in Q fever. Gastroenterology 1983;84:887-888.
230. Delsol G, Pellegrin M, Voigt JJ, et al: Diagnostic value of granuloma with fibrinoid ring. Am J Clin Pathol 1980;73:289.
231. Pellegrin M, Delsol G, Auvergnat JC, et al: Granulomatous hepatitis in Q fever. Hum Pathol 1980;11:51-57.
232. Moskovitz M, Fadden R, Min T: Human ehrlichiosis: A rickettsial disease associated with severe cholestasis and multisystemic disease. J Clin Gastroenterol 1991;13:86-90.
233. Nutt AK, Raufman J: Gastrointestinal and hepatic manifestations of human ehrlichiosis: 8 Cases and a review of the literature. Dig Dis 1999;17:37-43.
234. Sehdev AE, Dumler JS: Hepatic pathology in human monocytic ehrlichiosis: *Ehrlichia chaffeensis* infection. Am J Clin Pathol 2003;119:859-865.
235. Jackson MD, Kirkman C, Bradford WD, et al: Rocky mountain spotted fever: Hepatic lesions in childhood cases. Pediatr Pathol 1986;5:379-388.
236. Adams JS, Walker DH: The liver in Rocky Mountain spotted fever. Am J Clin Pathol 1981;75:156-161.
237. Walker DH, Staiti A, Mansueto S, et al: Frequent occurrence of hepatic lesions in boutonneuse fever. Acta Trop 1986;43:175-181.
238. Guardia J, Martinez-Vazquez JM, Moragas A, et al: The liver in boutonneuse fever. Gut 1974;15:549-551.
239. Mir-Madjlessi SH, Farmer RG, Hawk WA: Granulomatous hepatitis: A review of 50 cases. Am J Gastroenterol 1973;60:122-134.
240. Collins MH, Jiang B, Croffie JM, et al: Hepatic granulomas in children: A clinicopathologic analysis of 23 cases including polymerase chain reaction for histoplasma. Am J Surg Pathol 1996;20:332-338.
241. Smith JW, Utz JP: Progressive disseminated histoplasmosis: A prospective study of 26 patients. Ann Intern Med 1972;76:557-565.
242. Maekelt GA: Diagnostic procedures in the evaluation of hepatic diseases: Studies to determine mycotic etiology. Lab Res Methods Biol Med 1983;7:141-144.
243. Thaler M, Pastakia B, Shawker TH, et al: Hepatic candidiasis in cancer patients: The evolving picture of the syndrome. Ann Intern Med 1988;108:88-100.
244. Johnson TL, Barnett JL, Appelman HD, et al: Candida hepatitis: Histopathologic diagnosis. Am J Surg Pathol 1988;12:716-720.
245. Diebel LN, Raafat AM, Dulchavsky SA, et al: Gallbladder and biliary tract candidiasis. Surgery 1996;120:760-764, discussion 4-5.
246. Uflacker R, Wholey MH, Amaral NM, et al: Parasitic and mycotic causes of biliary obstruction. Gastrointest Radiol 1982;7:173-179.
247. Kates DM, Sparling TG, Jetha N, et al: Alteration of the natural history of *Pneumocystis carinii* infection in patients with acquired immunodeficiency syndrome receiving aerosolized pentamidine. West J Med 1991;154:721-723.
248. Boldorini R, Guzzetti S, Meroni L, et al: Acute hepatic and renal failure caused by *Pneumocystis carinii* in patients with AIDS. J Clin Pathol 1995;48:975-978.
249. Erdman SH, Barber BJ, Barton LL: Aspergillus cholangitis: A late complication after Kasai portoenterostomy. J Pediatr Surg 2002;37:923-925.
250. Padmanabhan S, Battiwalla M, Hahn T, et al: Two cases of hepatic zygomycosis in allogeneic stem cell transplant recipients and review of literature. Transplant Infect Dis 2007;9:148-152.
251. Marco del Pont J, De Cicco L, Gallo G, et al: Hepatic arterial thrombosis due to *Mucor* species in a child following orthotopic liver transplantation. Transplant Infect Dis 2000;2:33-35.
252. Mekeel KL, Hemming AW, Reed AI, et al: Hepatic mucormycosis in a renal transplant recipient. Transplantation 2005;79:1636.
253. Suh IW, Park CS, Lee MS, et al: Hepatic and small bowel mucormycosis after chemotherapy in a patient with acute lymphocytic leukemia. J Korean Med Sci 2000;15:351-354.
254. Oliver MR, Van Voorhis WC, Boeckh M, et al: Hepatic mucormycosis in a bone marrow transplant recipient who ingested naturopathic medicine. Clin Infect Dis 1996;22:521-524.
255. Tsui WM, Ma KF, Tsang DN: Disseminated *Penicillium marneffei* infection in HIV-infected subject. Histopathology 1992;20:287-293.
256. Duong TA: Infection due to *Penicillium marneffei,* an emerging pathogen: Review of 155 reported cases. Clin Infect Dis 1996;23:125-130.
257. Bonacini M, Nussbaum J, Ahluwalia C: Gastrointestinal, hepatic, and pancreatic involvement with *Cryptococcus neoformans* in AIDS. J Clin Gastroenterol 1990;12:295-297.
258. Das BC, Haynes I, Weaver RM, et al: Primary hepatic cryptococcosis. Br Med J Clin Res Ed 1983;287:464.
259. Sabesin SM, Fallon HJ, Andriole VT: Hepatic failure as a manifestation of cryptococcosis. Arch Intern Med 1963;111:661-669.
260. Bucuvalas JC, Bove KE, Kaufman RA, et al: Cholangitis associated with *Cryptococcus neoformans.* Gastroenterology 1985;88:1055-1059.
261. Knapp WA, Seeley TT, Ruebner BH: Fatal coccidioidomycosis: Report of two cases. Calif Med 1972;116:86-90.
262. Zangerl B, Edel G, von Manitius J, et al: Kokzidioidomykose als Ursache einer granulomatosen Hepatitis. Med Klin 1998;93:170-173.

263. Howard PF, Smith JW: Diagnosis of disseminated coccidioidomycosis by liver biopsy. Arch Intern Med 1983;143:1335-1338.
264. Ryan ME, Kirchner JP, Sell T, et al: Cholangitis due to *Blastomyces dermatitidis*. Gastroenterology 1989;96:1346-1349.
265. Teixeira F, Gayotto LC, De Brito T: Morphological patterns of the liver in South American blastomycosis. Histopathology 1978;2:231-237.
266. Bica I, Hamer DH, Stadecker MJ: Hepatic schistosomiasis. Infect Dis Clin North Am 2000;14:583-604.
267. Poltera AA, Katsimbura N: Granulomatous hepatitis due to *Strongyloides stercoralis*. J Pathology 1974;113:241-246.
268. Mondou EN, Gnepp DR: Hepatic granuloma resulting from *Enterobius vermicularis*. Am J Clin Pathol 1989;91:97-100.
269. Daly JJ, Baker GF: Pinworm granuloma of the liver. Am J Trop Med Hygiene 1984;33:62-64.
270. Garcia HH, Moro PL, Schantz PM: Zoonotic helminth infections of humans: Echinococcosis, cysticercosis and fascioliasis. Curr Opin Infect Dis 2007;20:489-494.
271. Filippou D, Tselepis D, Filippou G, et al: Advances in liver echinococcosis: Diagnosis and treatment. Clin Gastroenterol Hepatol 2007;5:152-159.
272. Craig P: *Echinococcus multilocularis*. Curr Opin Infect Dis 2003;16:437-444.
273. Lim JH: Toxocariasis of the liver: Visceral larva migrans. Abdom Imaging 2008;33:151-156.
274. Hartleb M, Januszewski K: Severe hepatic involvement in visceral larva migrans. Eur J Gastroenterol Hepatol 2001;13:1245-1249.
275. Kaushik SP, Hurwitz M, McDonald C, et al: *Toxocara canis* infection and granulomatous hepatitis. Am J Gastroenterol 1997;92:1223-1225.
276. Kaplan KJ, Goodman ZD, Ishak KG: Eosinophilic granuloma of the liver: A characteristic lesion with relationship to visceral larva migrans. Am J Surg Pathol 2001;25:1316-1321.
277. Inan M, Sakru N, Vatansever U, et al: Visceral larva migrans presenting as acute abdomen in a child. J Pediatr Surg 2006;41:e7-e9.
278. Berger T, Degremont A, Gebbers JO, et al: Hepatic capillariasis in a 1-year-old child. Eur J Pediatr 1990;149:333-336.
279. Arjona R, Riancho JA, Aguado JM, et al: Fascioliasis in developed countries: A review of classic and aberrant forms of the disease. Medicine (Baltimore) 1995;74:13-23.
280. MacLean JD, Graeme-Cook FM: Case records of the Massachusetts General Hospital: Weekly clinicopathological exercises. Case 12-2002: A 50-year-old man with eosinophilia and fluctuating hepatic lesions. N Engl J Med 2002;346:1232-1239.
281. Acosta-Ferreira W, Vercelli-Retta J, Falconi LM: *Fasciola hepatica* human infection: Histopathological study of sixteen cases. Virchows Archiv A Pathol Anat Histol 1979;383:319-327.
282. Marcos LA, Terashima A, Gotuzzo E: Update on hepatobiliary flukes: Fascioliasis, opisthorchiasis and clonorchiasis. Curr Opin Infect Dis 2008;21:523-530.
283. Lim JH, Kim SY, Park CM: Parasitic diseases of the biliary tract. AJR Am J Roentgenol 2007;188:1596-1603.
284. Al Absi M, Qais AM, Al Katta M, et al: Biliary ascariasis: The value of ultrasound in the diagnosis and management. Ann Saudi Med 2007;27:161-165.
285. Fogaca HS, Oliveira CS, Barbosa HT, et al: Liver pseudotumor: A rare manifestation of hepatic granulomata caused by *Ascaris lumbricoides* ova. Am J Gastroenterol 2000;95:2099-2101.
286. Stanley SL Jr: Amoebiasis. Lancet 2003;361:1025-1034.
287. Mikolajczak SA, Kappe SH: A clash to conquer: The malaria parasite liver infection. Mol Microbiol 2006;62:1499-1506.
288. Bhalla A, Suri V, Singh V: Malarial hepatopathy. J Postgrad Med 2006;52:315-320.
289. Maekelt GA: Diagnostic procedures in the evaluation of hepatic diseases: Studies to determine parasitologic etiology. Lab Res Methods Biol Med 1983;7:129-139.
290. Cruz I, Nieto J, Moreno J, et al: Leishmania/HIV co-infections in the second decade. Indian J Med Res 2006;123:357-388.
291. Albrecht H, Sobottka I, Emminger C, et al: Visceral leishmaniasis emerging as an important opportunistic infection in HIV-infected persons living in areas nonendemic for *Leishmania donovani*. Arch Pathol Lab Med 1996;120:189-198.
292. Malla N, Mahajan RC: Pathophysiology of visceral leishmaniasis: Some recent concepts. Indian J Med Res 2006;123:267-274.
293. Duarte MI, Corbett CE: Histopathological patterns of the liver involvement in visceral leishmaniasis. Rev Inst Med Trop Sao Paulo 1987;29:131-136.
294. Koshy A, Al-Azmi WM, Narayanan S, et al: Leishmaniasis diagnosed by liver biopsy: Management of two atypical cases. J Clin Gastroenterol 2001;32:266-267.
295. Tiwari I, Rolland CF, Popple AW: Cholestatic jaundice due to toxoplasma hepatitis. Postgrad Med J 1982;58:299-300.
296. Weitberg AB, Alper JC, Diamond I, et al: Acute granulomatous hepatitis in the course of acquired toxoplasmosis. N Engl J Med 1979;300:1093-1096.
297. Bonacini M, Kanel G, Alamy M: Duodenal and hepatic toxoplasmosis in a patient with HIV infection: Review of the literature. Am J Gastroenterol 1996;91:1838-1840.