# Chronic Hepatitis

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## Contents



## Abbreviations

| | |
|---|---|
| AIH | Autoimmune hepatitis |
| ALT | Alanine aminotransferase |
| APRI | AST-to-platelet ratio index |
| DAAs | Direct-acting antiviral agents |
| DNA | Deoxyribonucleic acid |
| HBcAg | Hepatitis B core antigen |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| HCC | Hepatocellular carcinoma |
| HCV | Hepatitis C virus |
| HDV | Hepatitis D virus |
| HIV | Human immunodeficiency virus |
| RNA | Ribonucleic acid |
| SVR | Sustained viral response |

Chronic viral hepatitis is defined as persistent inflammation of the liver in an identifiable hepatotropic viral (most commonly hepatitis B or C virus) infection persisting for 6 months or longer after acute infection [1]. Patients with chronic viral hepatitis may be asymptomatic or may complain of general fatigue, mild right hypochondoralgia, loss of appetite, nausea, and weakness. Many patients are diagnosed as having chronic viral hepatitis during routine physical with biochemical examination revealing abnormal liver chemistries, typically mild elevation of serum aminotransferases. Occasionally, patients may have flares or exacerbation of necroinflammatory activity in the liver, particularly with hepatitis B [2]. Less common causes of chronic viral hepatitis include hepatitis B/D coinfection and rarely chronic hepatitis E in immunosuppressed patients [3, 4].

The recent advances in noninvasive tests in the management of patients with chronic viral hepatitis—including elastography, radiologic studies, and serologic markers for fibrosis—have reduced the immediate need for liver biopsy, though an assessment of fibrosis is essential as those with advanced fibrosis and viral hepatitis are at high risk for complications from portal hypertension as well as hepatocellular cancer. Elastography is a method of assessing liver stiffness as a surrogate for liver fibrosis that uses longitudinal sound waves (transient elastography) or acoustic radiation forces [5, 6]. Elastography may also be determined by magnetic resonance. Imaging of the liver may also reveal a cirrhotic liver with an enlarged portal vein diameter, nodular liver, and splenomegaly which may be seen on ultrasound, CT scan with contrast, or MR with contrast.

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E. Hashimoto et al. (eds.), *Diagnosis of Liver Disease*, https://doi.org/10.1007/978-981-13-6806-6_5

Clinicians may also use any number of serum tests to assess fibrosis such as AST to platelet ratio index (APRI) or FIB-4 index using commonly available laboratory tests including AST, ALT, and platelet count. Finally, a number of commercial assays are also available worldwide to assess fibrosis.

However, despite all of these advances, liver biopsy is still considered the gold standard by many physicians in guiding the treatment of patients with chronic viral hepatitis, particularly in patients with chronic hepatitis B. In addition to providing staging and grading of chronic viral hepatitis, liver biopsy can furnish histologic information that is not availed by other tests. This is often the case in patients with comorbidities such as fatty liver, alcoholic, and iron storage diseases. Screening for hepatocellular carcinoma (HCC) may lead to fine needle aspiration or core biopsy of suspicious space-occupying lesions, especially lesions with atypical enhancement patterns that are suspicious for hepatocellular carcinoma as a late complication of chronic viral hepatitis that do not meet standard radiologic criteria for hepatocellular cancer. Depending on the underlying disease, the risks of HCC development may vary considerably. For example, chronic hepatitis B virus (HBV) is associated with the development of HCC in both cirrhotic and non-cirrhotic livers, whereas HCC rarely occurs in non-cirrhotic hepatitis C virus (HCV) infection. Therapy nucleoside analogues (and much less commonly interferon) have been shown to be most effective in suppressing HBV DNA levels, preventing fibrosis and reducing the risk of HCC [7, 8]. Direct-acting antiviral agents (DAAs) have replaced the combination of interferon with ribavirin as the standard therapy for chronic hepatitis C with high rates of cure (>95%) with minimal side effects [9].

Peritoneoscopy of a patient with chronic hepatitis generally shows an irregular surface of the tan-white liver, with or without red markings (Fig. 5.1). In general, chronic hepatitis is characterized by a combination of portal inflammation, interface hepatitis (previously referred to as piecemeal necrosis or periportal hepatitis), and mild lobular inflammation with scattered necroinflammatory foci. After years of continuous inflammation, fibrosis and cirrhosis may eventually develop.

Portal inflammation consists of lymphocytic infiltrate with a variable number of plasma cells. A mild degree of ductular reaction can be seen at the periphery of the portal tracts, which represents hepatic progenitor cell activation and correlates with the degree of interface hepatitis and fibrosis. Interface hepatitis is a common feature in chronic viral hepatitis, consisting of lymphocytic infiltrate at the limiting plate with associated necrosis or apoptosis of the periportal hepatocytes. This process results in the destruction of the periportal parenchyma, its replacement by fibrous tissue, stellate enlargement of the portal tracts, and portal-to-portal fibrous septum formation. The degree of interface hepatitis varies according to the activity of the disease; it is often focal or absent in mild disease activity. Focal ballooning degeneration of the periportal hepatocytes can be seen in severe interface hepatitis. Lobular inflammation in chronic viral hepatitis is typically variable in severity and spotty in distribution. Lymphocytes cluster around injured or apoptotic hepatocytes. In areas of hepatocyte necrosis, Kupffer cells may contain phagocytosed cellular debris. Lobular disarray, cholestasis, significant regeneration, and ballooning degeneration of the hepatocytes—similar to those seen in acute viral hepatitis—are uncommon in chronic viral hepatitis, unless there is severe exacerbation or injury due to other etiologies.

These histological features described above are not specific to chronic viral hepatitis; they are shared with other chronic liver diseases, most commonly autoimmune hepatitis (AIH), and drug-induced liver injury.

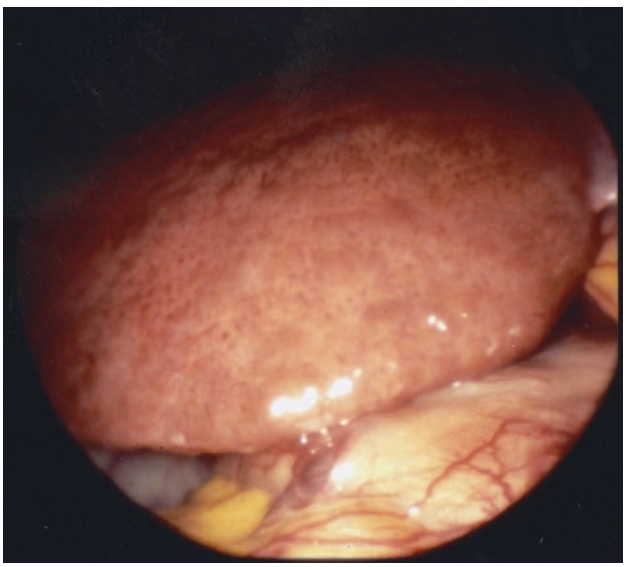

**Fig. 5.1** Peritoneoscopic findings of liver with chronic hepatitis. Peritoneoscopy shows tan-white liver with red markings on the surface

## 5.1 Hepatitis B Virus

Nearly 240 million people all over the world are chronic HBV surface antigen (HBsAg) carriers, with a large regional variation of HBsAg positive [10]. Chronic hepatitis B is characterized by various degrees of portal chronic inflammation, interface hepatitis, and lobular inflammation. The most distinctive histological feature of chronic hepatitis B is the presence of "ground-glass" hepatocytes (Fig. 5.2), which represents distended smooth endoplasmic reticulum containing abundant hepatitis B surface antigen (HBsAg). Ground-glass hepatocytes are seen in chronic hepatitis only and usually in biopsies that show minimal necroinflammatory activity and represent a marked increase of smooth endoplasmic reticulum which contains filamentous and spherical HBsAg particles. The accumulation of hepatitis B core antigen (HBcAg) within the hepatocyte nuclei produces the sanded nucleus appearance. Intrahepatic HBcAg positivity may correlate with a higher degree of necroinflammatory activity [11].

The distribution of both HBV core and surface antigens and the subcellular localization of HBsAg in liver biopsy of patients with chronic hepatitis B and cirrhosis can be examined using immunohistochemistry and ultrastructural immunoperoxidase techniques. The distribution patterns of HBsAg in hepatocytes are membranous, cytoplasmic, festoon, and inclusion body types (Fig. 5.3). Both cytoplasmic and festoon types are seen more frequently than the membranous type. Extensive membranous staining for HBsAg is usually parallel to the staining of core antigen and associated with high viral replication. HBcAg is found predominantly in the nucleus and less prominently in the cytoplasm of hepatocytes, and electron microscopy shows clusters of HBV particles in the nucleus (Fig. 5.4). HBcAg immunoreactivity is detected in HBsAg-positive hepatocytes, and the staining pattern of HBsAg is the festoon and cytoplasmic type (Fig. 5.5). The inclusion body pattern of HBsAg is characteristic of liver cirrhosis with HCC, which suggests active syn-

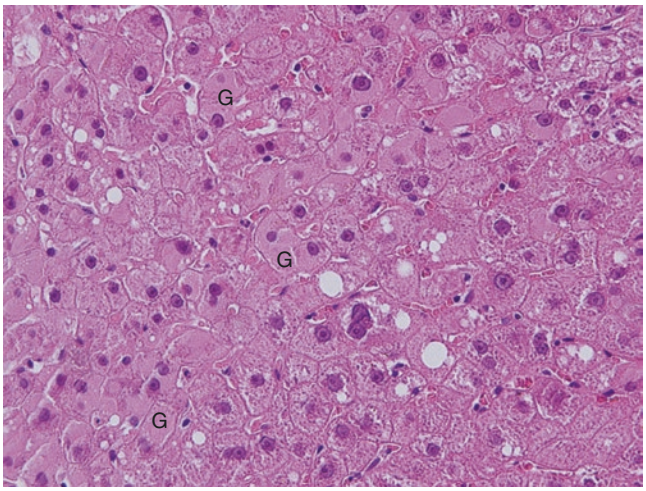


**Fig. 5.2** Ground-glass hepatocytes (G) in chronic hepatitis B. Finely granular pink inclusions are identified in hepatocytes. Many ground-glass hepatocytes show a pale-staining halo in the cytoplasm

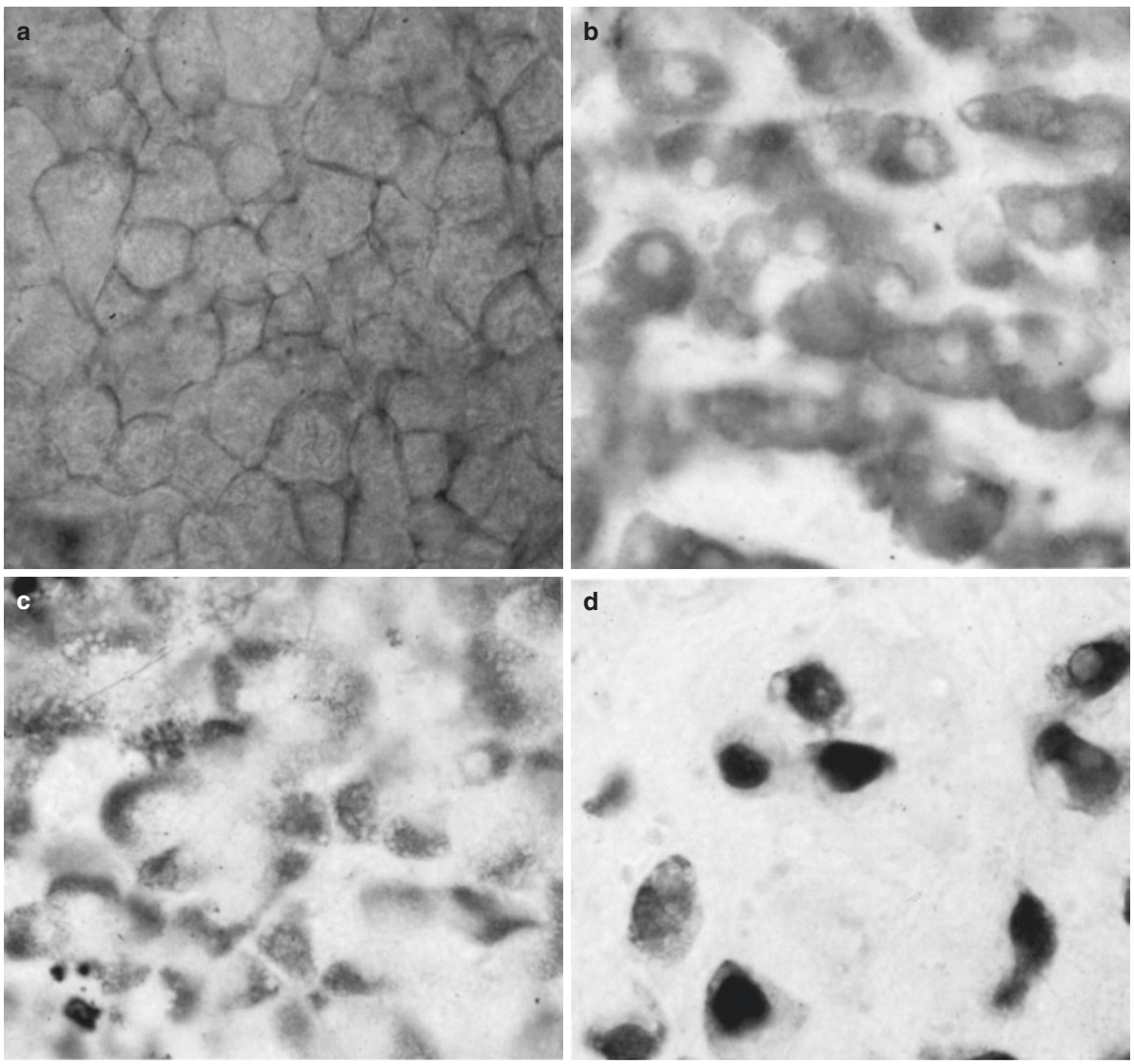


**Fig. 5.3** HBsAg staining patterns. HBsAg localization reveals the membranous (**a**), cytoplasmic (**b**), festoon (**c**), and inclusion type (**d**)

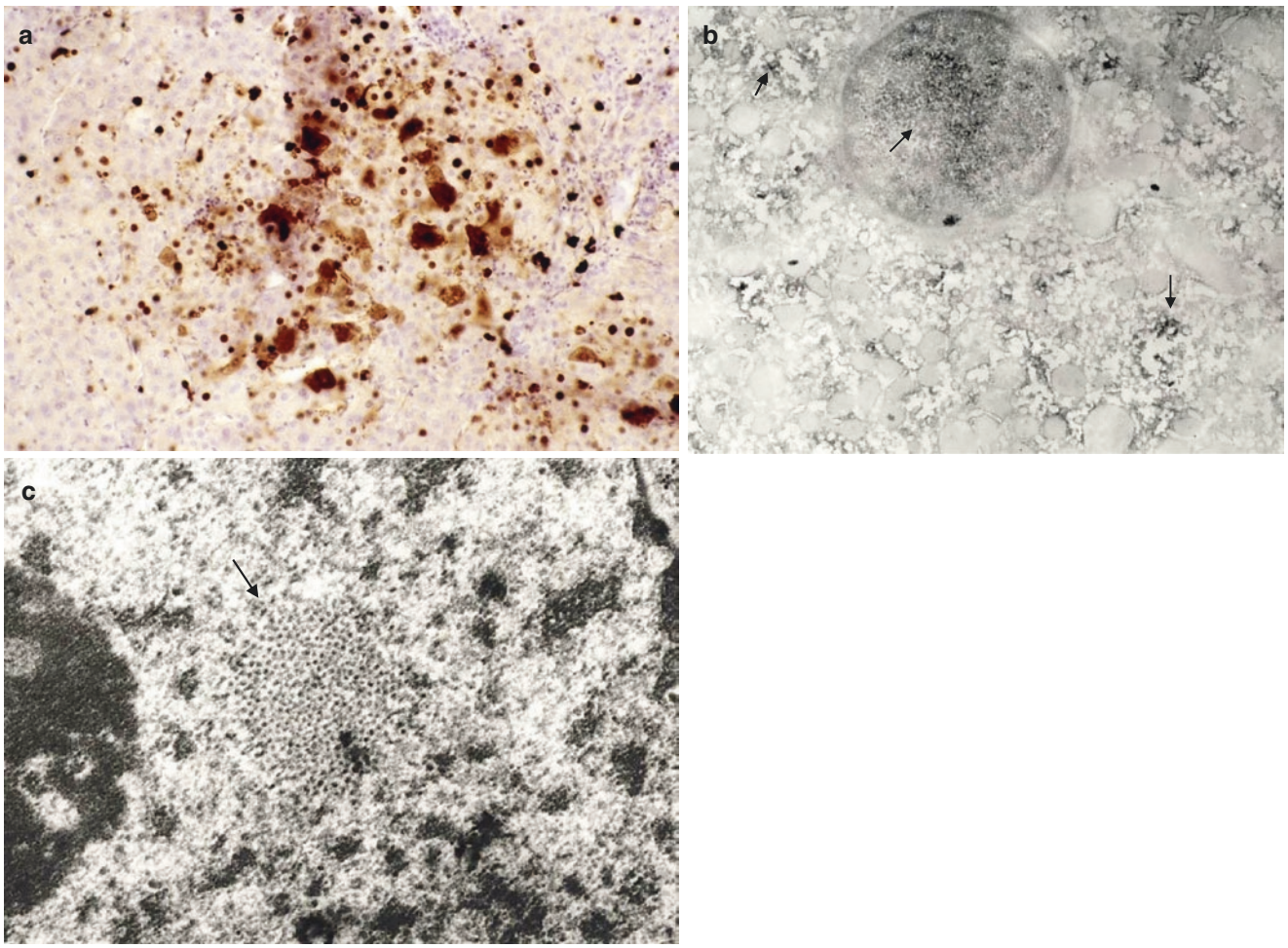


**Fig. 5.4** HBcAg. (**a**) HBcAg immunoreactivity is seen not only in the nucleus of hepatocytes but also in the cytoplasm. (**b**) Immunoelectron microscopy shows the presence of HBcAg (arrow) in the nucleus and cytoplasm. (**c**) Electron microscopy shows a cluster of hepatitis B virus particles (arrow) in the nucleus

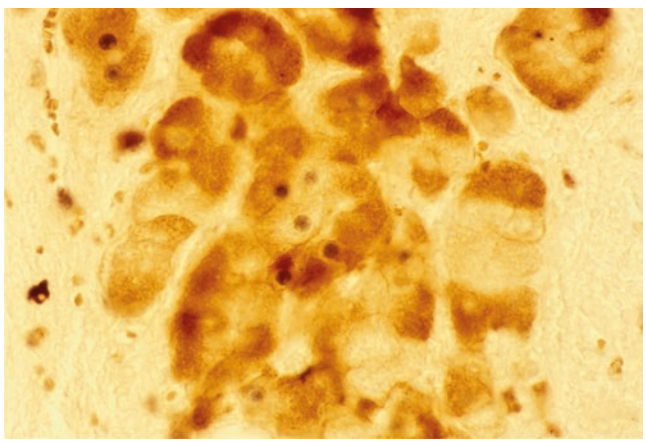

**Fig. 5.5** Co-localization of HBsAg and HBcAg. Double staining shows the presence of HBcAg (purple) in the nucleus or cytoplasm of hepatocytes with cytoplasmic and festoon type of HBsAg (brown)

thesis of HBsAg in chronic hepatitis or cirrhosis, and that HBV is retained in the liver with HCC.

Hepatitis B treatments depend on E antigen status, extent of liver injury, HBV DNA level, and ALT level. For HBeAg-positive patients with elevated ALT (ALT more than twice the upper limit), the HBV threshold of treatment is 20,000 IU/L, and for HBeAg-negative patients with elevated ALT, HBV threshold of treatment is 2000 IU/L. In addition, AASLD suggests antiviral therapies to reduce the risk of perinatal transmission of hepatitis B in HBsAg-positive women with an HBV level >200,000 IU/mL. Approved agents for hepatitis B therapies include tenofovir disoproxil, tenofovir alafenamide, entecavir, telbivudine, adefovir, and lamivudine [2, 12, 13]. Interferon may also be given for a finite duration with lower rates of viral suppression but, in general, higher rates of HBeAg clearance and HBsAg clearance.

Hepatitis D virus (HDV, delta agent) superinfection requires HBsAg, and this phenomenon can be demonstrated using immunohistochemical stains. The clue to HDV infection is severe necroinflammatory activity in patients with HBV; therefore, HDV infection should be suspected in all patients with hepatitis B who develop severe exacerbation of disease activity or who have a severe clinical course. Diagnosis is confirmed via positivity for anti-HDV in a patient seropositive for HBsAg and/or quantitative/qualitative testing for serum HDV RNA. There are no approved therapies for hepatitis D though interferon has been used.

Fibrosing cholestatic hepatitis, an atypical form of chronic hepatitis B infection, may be encountered in patients with HIV infection or in immunosuppressed states, such as post-liver transplantation [14]. It is caused by the direct cytopathic effect of hepatitis B, seen in the high levels of HBV replication and massive HBcAg expression in the liver. The histological features include marked ductular reaction at the limiting plate, combined with cholangiolitis and extensive periportal sinusoidal fibrosis. With the advent of nucleoside/nucleotide analogues, fibrosing cholestatic hepatitis is readily treated.

## 5.2 Hepatitis C Virus

The total global HCV prevalence is estimated at 2.5% with an approximate 70 million of HCV RNA positive cases [15]. There are six main genotypes of hepatitis C; genotype 1b is the most common genotype worldwide followed by genotype 3 [16].

Most cases of chronic hepatitis C tend to show mild necroinflammatory activity on biopsies. The portal tract is infiltrated by dense aggregates of lymphocytes with follicle formation; the intralobular bile ducts are often found within the lymphocytic infiltrate and disrupted; and mild macro vesicular steatosis can be seen in the lobule, particularly in periportal hepatocytes (Fig. 5.6) [17, 18]. The lobular necroinflammatory activity is commonly represented by scattered acidophilic or apoptotic bodies in the lobules.

Steatosis in chronic hepatitis C can occur in the periportal or centrilobular region or both. Although steatosis tends to occur in hepatitis C genotype 3b infection [12], excessive centrilobular steatosis in genotype 3 or other genotypes may suggest concurrent steatohepatitis. Hepatitis C genotype 3

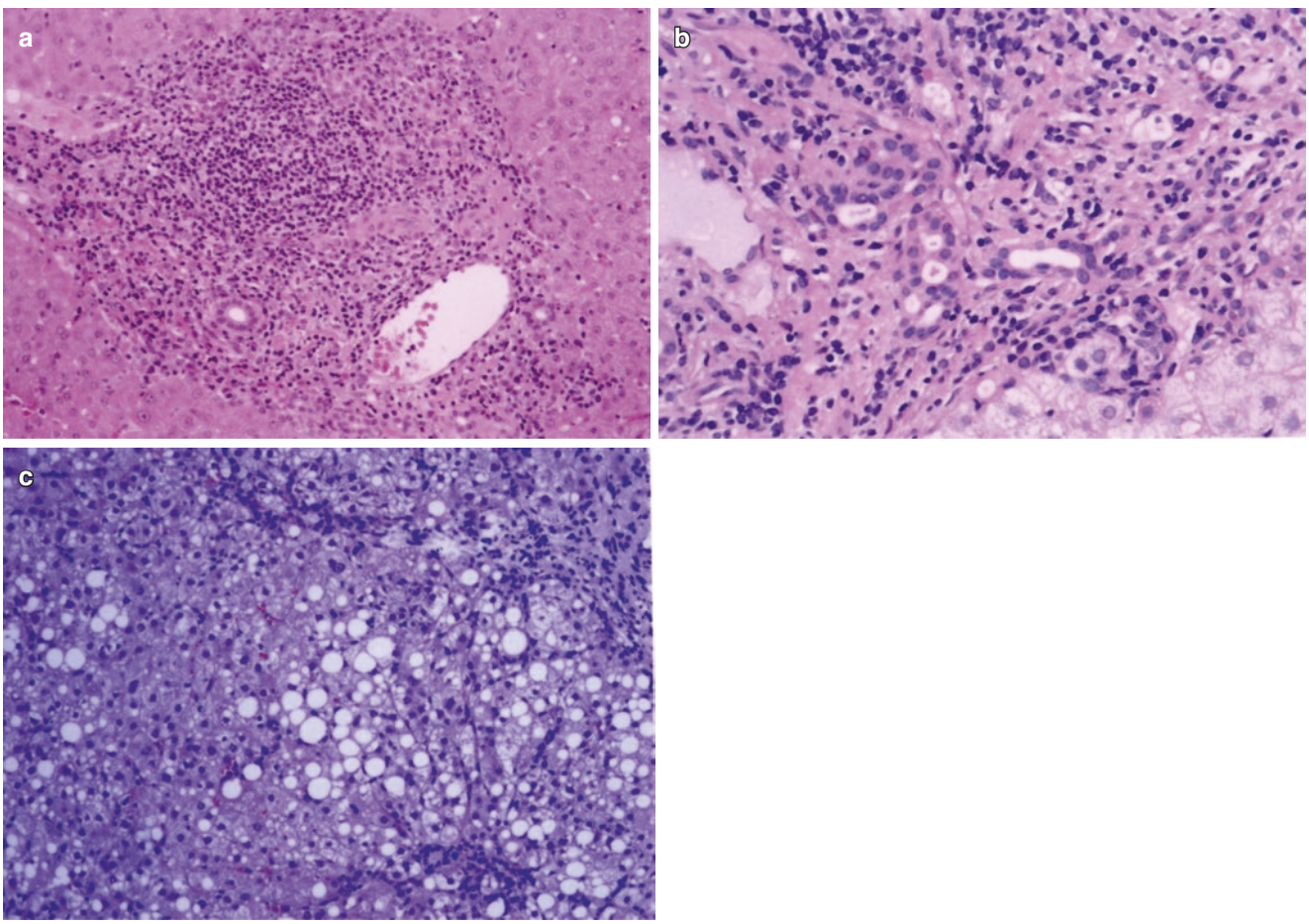


**Fig. 5.6** Histological features of chronic hepatitis C. (**a**) The formation of lymphoid follicles is observed in the portal tract. (**b**) Bile duct damage is seen in the portal tract. (**c**) Steatosis is seen around the portal tract

also has the most aggressive natural history (fibrosis progression as well as HCC risk) [19].

Treatment for hepatitis C is recommended for all patients with chronic HCV infection, except those with short life expectancies owing to comorbid conditions. Agents currently used for hepatitis C treatment include ribavirin and direct-acting antiviral agents (DAAs) [20, 21]. The treatment regimen is selected based on the genotype, extent of liver damage, and response to previous treatment. There are multiple DAAs available for treatment. These agents belong to multiple classes and are combined to achieve high rates of cure: NS3 protease inhibitors, NS5A replication complex inhibitors, and NS5B polymerase inhibitors (sofosbuvir). DAAs have been proved very effective in multiple trials achieving a sustained viral response (SVR) or cure of greater than 95% of infected individuals even in genotype 3.

Hepatitis C may induce autoantibody formation, including antinuclear and anti-LKM type 1, but the titers are low. Clinically, these patients still resemble patients with chronic hepatitis C and not AIH. The presence of severe activity and a significant number of plasma cells—in the area of interface hepatitis in a liver biopsy specimen of a patient with chronic hepatitis C—suggest concurrent autoimmune features that are induced either by the HCV infection or by the interferon treatment. The overlap syndrome of AIH and chronic hepatitis C implies the coexistence of AIH with high titer of autoantibodies and high IgG level and detectable HCV RNA [22]. The diagnosis of AIH alone should not be rendered to patients who are known to harbor the virus, as corticosteroid therapy will enhance viral replication and disease progression. In the era of DAA therapy, it is now straightforward to treat hepatitis C patients with DAAs first to see if liver chemistries normalize and, if they do not, address the potential AIH.

In chronic hepatitis C, the rate of progression to cirrhosis correlates with serum HCV RNA levels, high-grade necroinflammatory activity, and advanced stage at initial biopsies [23, 24]. Other factors that may influence disease progression include viral genotype, sex, age, alcohol consumption, and iron overload. Genotype 3 is harder to treat in the era of DAAs though SVR rates still are excellent. Male and older individuals are more likely to show progressive fibrosis. Alcohol consumption increases viral replication and severity of disease. Iron overload may reduce the response to antiviral therapy.

Late complications of chronic hepatitis C infection include diabetes, cirrhosis with or without decompensation, lymphoma, hepatocellular cancer (HCC), and less commonly intrahepatic cholangiocarcinoma [25].

## 5.3 Hepatitis E Virus

There are 20 million HEV infections estimated worldwide, further leading to an estimated 3.3 million symptomatic cases of hepatitis E [26]. Hepatitis E is usually considered as a self-limiting illness lasting 1–3 months with spontaneous resolution. However, recent studies suggested that there is virus retention in posttransplant immunocompromised patients. HEV genotypes 3 and 4 can lead to chronic infection in transplant recipients and immunosuppressed subjects. Worsening of liver function, liver cirrhosis, and decompensation due to chronic HEV infection can occur as early as 2 years after infection with hepatitis E [27]. A 3-month course of ribavirin is recommended as treatment if an immunocompromised patient fails to clear the virus in 3 months after detection. If the patient has a detectable viral load after 3 months of ribavirin, a 6-month course of ribavirin is given. Pegylated interferon for 3 months has been used if ribavirin therapy fails.

## 5.4 Combined Viral Infection

Hepatitis B and C or hepatitis B/C and HIV coinfection is not uncommon due to shared modes of transmission [28]. In hepatitis B and C coinfection, the features of hepatitis C often predominate. If co-replication occurs, the disease is more likely to be severe and show faster progression of fibrosis.

HIV coinfection negatively impacts on the natural history of acute and chronic viral hepatitis, thereby increasing the risk of chronicity and progressive liver disease [29]. In addition, drug-induced liver injury related to antiretroviral therapy complicates the treatment of both diseases and should be considered in "exacerbation" or atypical presentation of chronic viral hepatitis. Treatment for coinfected patients is similar to monoinfected patients; drug-drug interactions must be accounted for, particularly with HIV/HCV coinfection with similar high rates of efficacy.

## 5.5 Non-viral Causes of Chronic Hepatitis

In most cases, chronic hepatitis is caused by hepatitis viruses B, C, and B/D; rare isolated cases are caused by non-hepatitis viruses (Epstein-Barr virus and cytomegalovirus), bacterial infection, and parasitic infestation [30–32]. Steatohepatitis due to metabolic syndrome is likely the most common form of non-viral chronic hepatitis worldwide [33]. Toxic substances such as alcohol, drugs, and chemicals also cause chronic hepatitis. Genetic and metabolic etiologies are relatively rare but should be taken into account. Chronic hepatic autoimmunopathies including AIH, primary biliary cirrhosis, primary sclerosing cholangitis, and overlap syndrome are more frequent than has hitherto been assumed.

AIH is reported to be due to disturbance of the immune system. Immunologically, it is classified into two types, of which type 1—with antinuclear antibody or anti-smooth muscle antibody-positive sera—is most frequent in AIH [34]. All AIH types are treated with administration of pred-

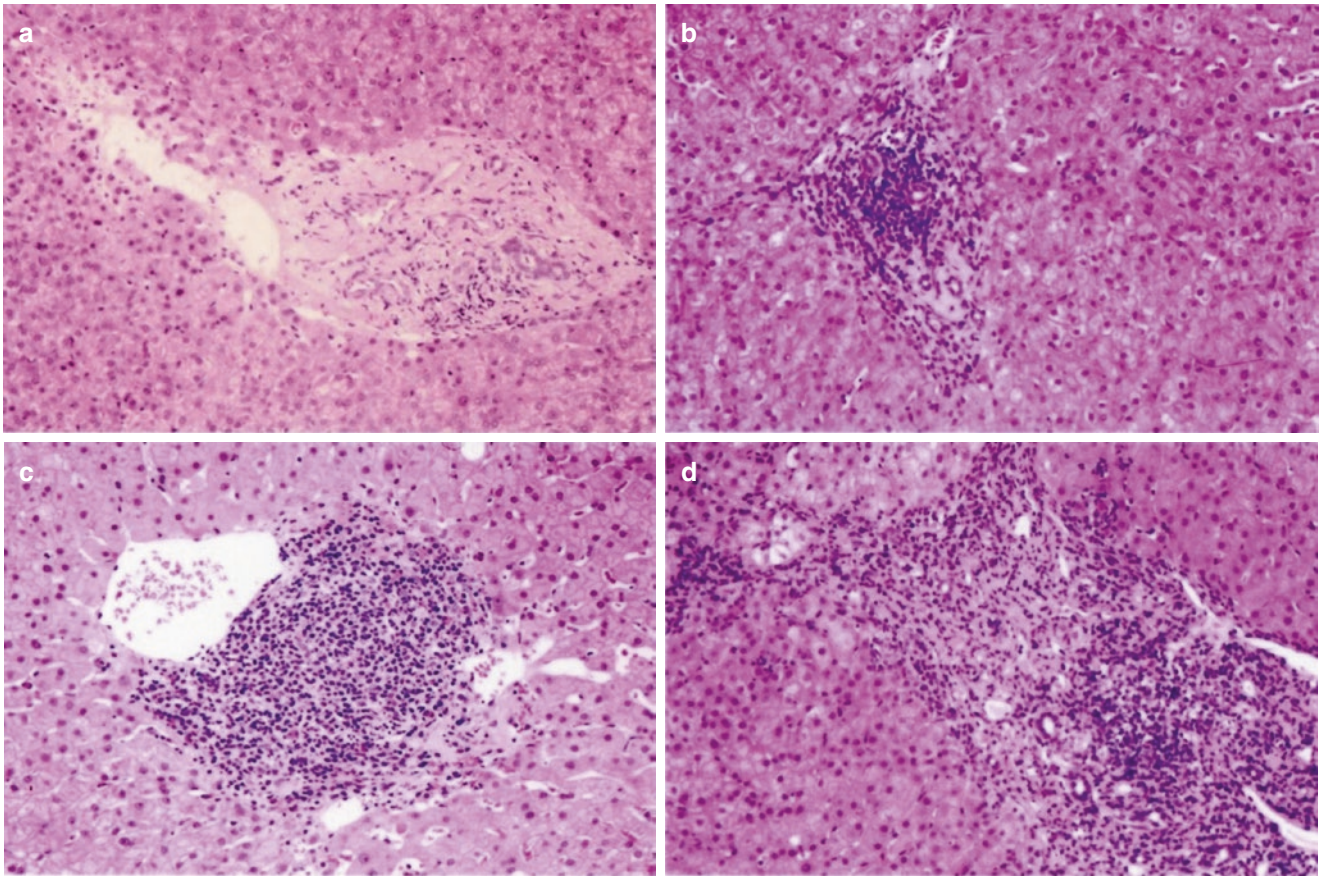


**Fig. 5.7** Grading of inflammation in chronic hepatitis C. (**a**) No inflammation is observed in the portal tract, and necrosis is not seen in the lobule. (**b**) Mild inflammation is seen in the portal tract with minimal interface hepatitis. (**c**) Mild interface hepatitis with lymphoid follicle is seen in the portal tract. (**d**) Moderate interface hepatitis is seen, with the establishment of bridging fibrosis

nisolone with or without immunomodulators, and most individuals respond well. However, few cases that do not respond to prednisolone require high dosage or a combination with other immunomodulators. Cirrhosis may rapidly occur when the patient does not respond well to immunotherapy or when the diagnosis and therapy of AIH are delayed. Interface hepatitis with infiltration of lymphoplasmacytic cells is histologically characteristic of AIH, and lobular necrosis is frequently seen after acute onset, while bridging necrosis and fibrosis are observed in the chronic phase of AIH (Fig. 5.7). Cirrhotic change develops in asymptomatic patients when AIH is diagnosed.

## 5.6 Staging and Grading of Chronic Hepatitis

Several semiquantitative scoring systems were introduced over the years, including those of Knodell in 1981 [35], Scheuer in 1991 [36], Ishak in 1995 [1], Ludwig and Batts in 1995 [37], and METAVIR in 1996 [38]. Each system has its strengths and weaknesses in clinical practice or in investigative work. The Ishak system is often used in clinical trials, while the newer systems are simple to understand and allow greater reproducibility in everyday clinical practice.

Grading pertains to the intensity of inflammation. For example, according to the Ludwig and Batts system, a score of 0 indicates the absence of inflammation while 1 refers to minimal portal and lobular inflammation, 2 refers to mild or localized interface hepatitis and/or mild lobular inflammation, 3 refers to moderate or more extensive interface hepatitis and/or moderate lobular inflammation, and 4 indicates severe and widespread interface hepatitis (Fig. 5.8).

Staging refers to the degree of fibrosis and is also measured on a semiquantitative scale ranging from 0 to 4, with 0 indicating the lack of fibrosis while 1 refers to fibrosis confined to the portal tract, 2 refers to periportal or portal-to-portal septa, 3 refers to bridging fibrosis causing structural distortion (but without obvious cirrhosis), and 4 refers to cirrhosis (Fig. 5.9).

It is important to understand that the use of a scoring system for staging and grading is not meant to replace microscopic description and should include diagnosis of concurrent comorbidities, such as fatty liver and alcoholic and metabolic diseases, which may alter treatment decisions.

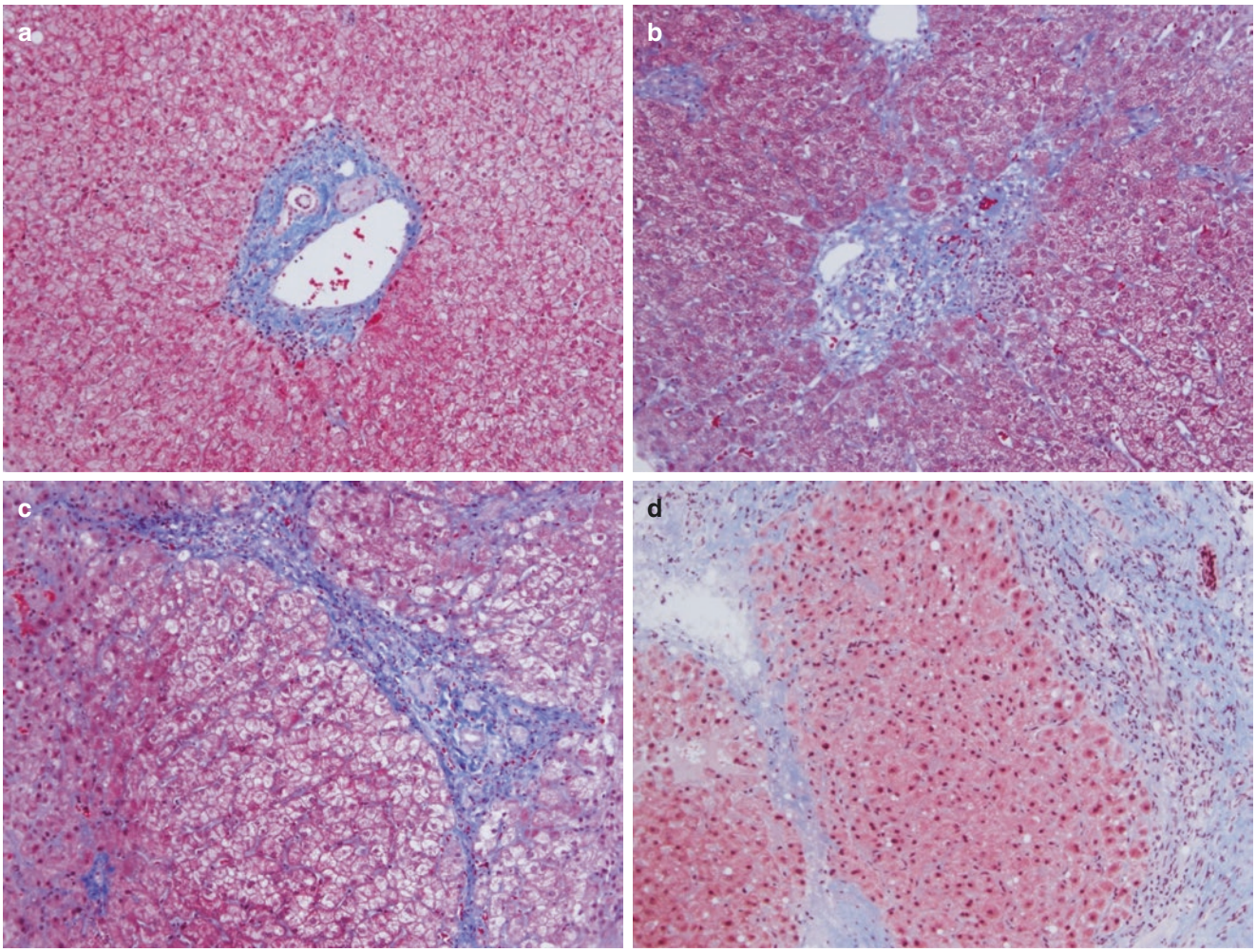


**Fig. 5.8** Stages of chronic hepatitis C (Masson's trichrome stain). (**a**) Stage 1 = Localized fibrosis is seen in the portal tract. (**b**) Stage 2 = Portal fibrosis extends beyond the portal tract. (**c**) Stage 3 = Portal fibrosis extends beyond the portal tract, bridging fibrosis is seen, and the lobular structure is distorted. (**d**) Stage 4 = Pseudolobular formation is seen

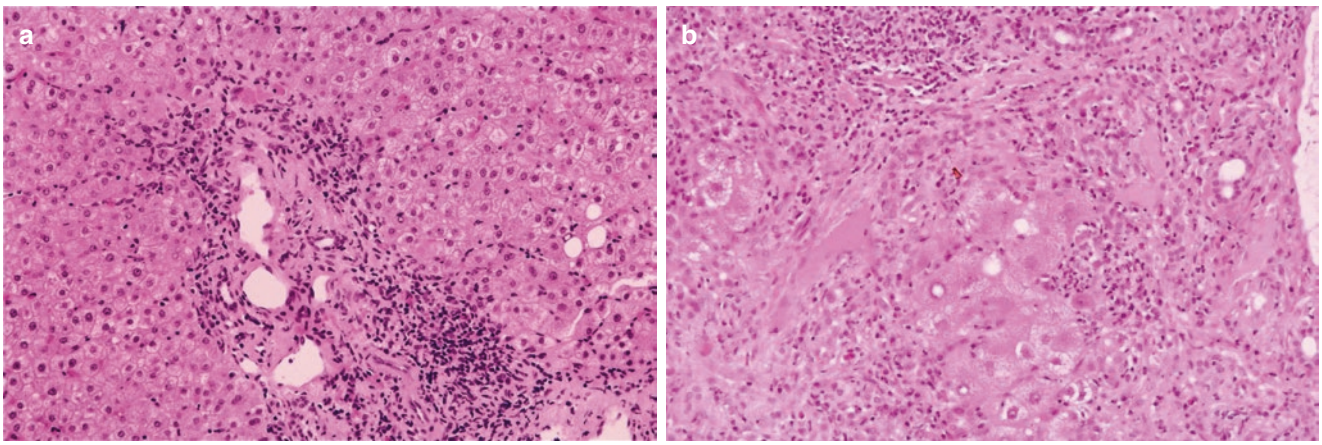


**Fig. 5.9** Autoimmune hepatitis (AIH) . (**a**) Interface hepatitis is seen, with infiltration of lymphoplasmacytic cells in AIH. (**b**) Bridging necrosis is observed in the chronic phase of AIH. (**c**) Intralobular necrosis is present with a cluster of lymphoplasmacytic cells, and rosette formation of hepatocytes is seen. (**d**) Bridging fibrosis develops simultaneously (Mallory-Azan stain)

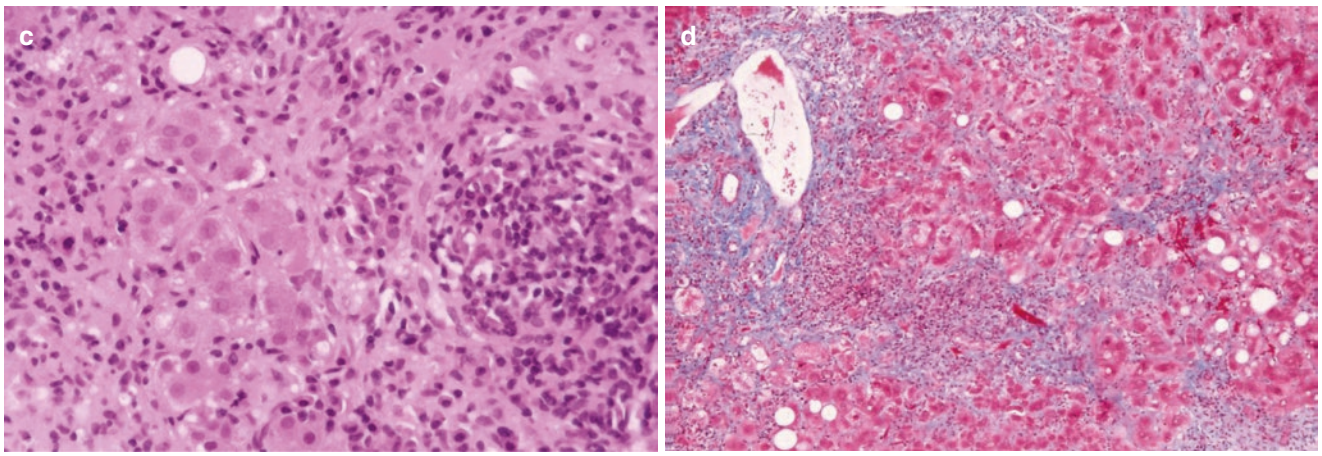


**Fig. 5.9** (continued)

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