Chronic Hepatitis C and Direct Acting Antivirals

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KEYWORDS

• Hepatitis C • Directly acting antivirals • Transient elastography • Liver biopsy • Diagnostic criteria • Histology

Key points

- HCV is the most common blood borne viral infection in the United States.
- HCV patients with comorbidities, such as alcohol use, NASH, and hepatitis B coinfection are more likely to undergo liver biopsy. Hence, pathologists should keep in mind that concomitant effects of these factors may be seen on histology.
- Histologic features of chronic HCV hepatitis include dense lymphoid aggregates in the portal tracts with mild interface activity. Severe necroinflammatory activity is unusual in chronic HCV and should prompt consideration of another or additional disease entity.
- Cure rates with direct acting antivirals are now more than 90% in most cases. The risk for HCC, however, still persists and underscores the need for continued HCC surveillance.
- Persistent inflammation may be found even after achieving sustained virologic response due to treatment. Regression of fibrosis can also occur.

ABSTRACT

The hepatitis C virus (HCV) is the most common blood-borne infection in the United States and is the most common cause of end-stage liver disease requiring liver transplant. Over the last 10 years, direct acting antiviral therapies have revolutionized HCV treatment, increasing the cure rates from less than 50% to more than 90% in those who reach access to care. This article is an overview for pathologists and clinicians covering the histologic findings of HCV as well as direct acting antiviral therapy.

HEPATITIS C VIRUS OVERVIEW

The hepatitis C virus (HCV) is the most common blood-borne infection in the United States, affecting up to 3.5 to 4 million Americans.[1] It is also the most common cause of end-stage liver disease requiring liver transplant.[2] HCV poses an underrecognized public health challenge and remains undiagnosed in most of those infected (up to 70%).[3,4] Furthermore, since 2007, HCV has surpassed the human immunodeficiency virus (HIV) as a cause of death in the United States, and contributed to a growing health care access and outcome disparity because it disproportionately affects those who are homeless, living below the poverty level, incarcerated, or with a history of injection drug use or alcohol abuse. The irony is that over the last 10 years, a revolution in HCV treatment with directly acting antiviral (DAA) therapies has occurred, increasing the cure rates from less than 50% to more than 90% in those who are able to traverse gaps in current practice from infection to diagnosis to access to care. This article provides an overview of HCV for pathologists and clinicians with a specific focus on DAAs and histologic findings of HCV.

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Surgical Pathology ■ (2018) ■–■
https://doi.org/10.1016/j.path.2018.02.002

RISK FACTORS FOR HEPATITIS C VIRUS

Risk factors for HCV are well known, including injection drug use, high-risk sexual exposures, blood transfusions, tattoo placement, hemodialysis, occupation as a health care worker, and vertical transmission. Risk factors for progression of hepatic fibrosis include host factors, such as older age at infection, male gender, duration of infection, iron overload (hemochromatosis), and most importantly and within patient control, alcohol and tobacco use. Other factors include immunosuppression; hepatic steatosis associated with alcoholic and nonalcoholic fatty liver disease; diabetes mellitus (DM); coinfection with hepatitis B virus (HBV); and viral factors, such as genotype 3 and alanine aminotransferase (ALT) elevation as shown in **Box 1**.[5] Given the growing prevalence of nonalcoholic steatohepatitis (NASH) in the United States, providers must be aware of the concomitant risk it poses on those already infected with HCV in increasing the risk of hepatic fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Furthermore, it is important for pathologists to recognize that it is these patients with comorbidities, such as alcohol use, NASH, DM, and HBV, or HIV coinfection who are more likely to undergo a biopsy of the liver, so that assessment for and awareness of concomitant effects of these factors are taken into account on histologic interpretation.

Box 1
Factors influencing liver fibrosis

Host
- Duration of infection
- Age at infection greater than 40 years old
- Gender (male)

Toxins
- ETOH consumption
- Tobacco/cannabis use
- Iron overload

Immunosuppression
- HIV coinfection
- Organ transplant

Liver-related factors
- HBV coinfection
- ALT elevation
- Fibrosis
- Genotype 3

Metabolic factors
- Steatosis
- Insulin resistance

Viral load is NOT predictive

From Feld JJ, Liang TJ. Hepatitis C: identifying patients with progressive liver injury. Hepatology 2006 43(S1): S195; with permission.

The incubation period of HCV is on average 6 to 8 weeks, and only a small minority (~20%) of patients present symptomatically with nonspecific complaints of malaise or fatigue, with only rare development of jaundice. Chronic infection occurs in approximately 60% to 85% of those acutely infected, but once established, the natural history of HCV is progressive. Over a period of 20 to 40 years, patients with chronic HCV progress to cirrhosis in at least 20%. Once cirrhosis is established, the risk of HCC remains elevated at more than 1% to 4% a year, and the risk of hepatic decompensation at 3% to 6% per year. Patients with HCC or hepatic decompensation face a high risk of death without liver transplantation.[6–8] Despite the recent groundbreaking strides in DAA development, the United States still faces the prospect of an important incidence of decompensated cirrhosis and HCC as a result of the aging of the "Baby Boomers" (born between 1945–1965), who have a more than three-fold higher prevalence of HCV than the rest of the US population, and thus are at a higher risk for such HCV complications.[9]

Like those with acute infection, most patients with chronic HCV hepatitis have no symptoms, with gradual and incremental development of fatigue as the main complaint, until cirrhosis and end-stage liver disease develop, at which point ascites, hepatic encephalopathy, and jaundice can occur. Extrahepatic manifestations of HCV include mixed cryoglobulinemia, porphyria cutanea tarda, polyarteritis nodose, and association with DM and lymphoma (**Fig. 1**).

Abnormal liver function tests are the most common mode of alerting providers to the presence of HCV infection, and thus, the Centers for Disease Control and Prevention has recommended testing for HCV in those at risk, including those with injection drug use history, abnormal liver enzymes, and those born between 1945 and 1965 (**Box 2**).[10] A positive anti-HCV antibody indicates exposure to HCV but does not distinguish between active or resolved infection, and is also not protective toward reinfection. Because false-positive serologic testing can occur, it is imperative for a confirmatory HCV RNA test to be performed.[11] An HCV genotype is then obtained to guide treatment