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CLINICAL MANIFESTATIONS OF HEPATITIS C: A NARRATIVE REVIEW

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ABSTRACT
Hepatitis C, caused by the Hepatitis C virus (HCV), presents a wide range of clinical manifestations, from asymptomatic cases to severe liver disease. Acute Hepatitis C infection is often asymptomatic or presents with mild, non-specific symptoms such as fatigue, anorexia, mild abdominal pain, and jaundice. Approximately 15-25% of individuals may spontaneously clear the virus during the acute phase.
Chronic Hepatitis C, developing in about 75-85% of those infected, often remains asymptomatic for decades. During this prolonged asymptomatic phase, HCV gradually causes hepatic inflammation and fibrosis. Clinical manifestations of chronic Hepatitis C are typically subtle and nonspecific, including persistent fatigue, malaise, and intermittent right upper quadrant discomfort. As the disease progresses, more severe hepatic involvement

can lead to complications such as cirrhosis and hepatocellular carcinoma (HCC).
Cirrhosis, a significant long-term consequence of chronic HCV infection, may present with jaundice, ascites, splenomegaly, easy bruising or bleeding, and encephalopathy. Patients with cirrhosis are at increased risk for developing liver failure and HCC, the latter presenting with symptoms such as weight loss, anorexia, and a palpable liver mass. Extrahepatic manifestations of Hepatitis C, affecting up to 40% of patients, include mixed cryoglobulinemia, which can lead to vasculitis, renal disease, and peripheral neuropathy. Other systemic conditions associated with HCV include insulin resistance, type 2 diabetes mellitus, and lymphoproliferative disorders such as non-Hodgkin lymphoma.
The clinical course of Hepatitis C varies widely among individuals, influenced by factors such as the patient's age, sex, duration of infection, viral genotype, co-infections (e.g., HIV), and comorbid conditions, including alcohol use and metabolic syndrome. Advances in antiviral therapies, particularly direct-acting antivirals (DAAs), have revolutionized the management of Hepatitis C, offering the potential for viral eradication and significant reduction in disease-associated morbidity and mortality. Continuous research and public health efforts are essential to improve screening, diagnosis, and treatment outcomes for individuals affected by Hepatitis C.
Keywords: Hepatitis C virus, fatigue, abdominal pain, direct-acting antivirals.

INTRODUCTION

The National Institutes of Health examined every instance of acute hepatitis C from 1994 to 2007 using a retrospective cohort analysis. Twenty-five patients (16 girls and 9 men) were observed under routine care. The cohort, which had an average exposure age of 43 years (range: 20-72 years), consisted of 17 Caucasians (three of them were Hispanic and one Native American), 6 African Americans, and 2 Asians. Forty percent of the patients had symptoms, and eighty percent of them had jaundice. Fatigue (68%), dark urine (60%), abdominal discomfort (60%), chills and low-grade fever (44%), appetite loss (40%), itching (36%), muscular aches (36%), mood swings (32%), joint pain (24%), dyspepsia (16%), diarrhea, and disorientation (8% each) were among the most common symptoms. The most common clinical symptom, observed in 40% of individuals, was jaundice. Following antiviral therapy and HCV RNA elimination, two patients who had acute liver failure with hepatic encephalopathy and ascites recovered. Furthermore, one patient developed a maculopapular rash, while two others reported having acne. According to test results, peak bilirubin levels above 2.5 mg/dL in 44% of patients and ALT levels exceeded 10 times the upper limit of normal (ULN) in 70% of patients. The two individuals who had ascites and encephalopathy had elevated prothrombin times. Eighty percent of patients had verified anti-HCV seroconversion, while the remaining twenty percent had anti-HCV positive status at the time of presentation (1).

Forty patients (68% males, 73% White, aged 18-75 years) with probable acute hepatitis C were enrolled at the Philadelphia VA Medical Centre between 2000 and 2010. Sixty percent of the individuals developed jaundice with total bilirubin levels ≥3 mg/dL, and all subjects had increased ALT levels. Of the patients, 43% experienced severe liver inflammation and/or jaundice; 13% had ALT levels greater than 1000 U/L and 28% had total bilirubin levels greater than 10 mg/dL (2).

A cohort of 214 Italian patients with newly confirmed hepatitis C was investigated between 1999 and 2004. The cohort was dispersed throughout the islands of northern Italy (38.8%), middle Italy (18.7%), and southern Italy (42.5%). 37.5 was the average age, and 65.4% of the population was male. After the disease began, HCV RNA cleared in 71 days (range: 27–173), with 80% of individuals with self-limiting hepatitis doing so in three months. Of the patients, 68% had symptomatic illness; 57% had jaundice and 12% had bilirubin levels higher than 10

mg/dL. 73% of patients had ALT levels that were 20 times higher than the ULN, and 18% had levels that were 50 times higher (3).

Nine patients with acute hepatitis C were found at the University of California, San Francisco between 2002 and 2004. Both asymptomatic and symptomatic HIV-positive individuals were included in this investigation; the infections were detected by seroconversion or elevated blood transaminase levels. Seven individuals experienced flu-like symptoms, nausea, abdominal discomfort, and jaundice; two of them needed to be hospitalized because of severe symptoms and liver malfunction. The majority of individuals had HIV under control when they were diagnosed with HCV (4).

The mean age of hepatitis C patients in another study was 57.3 years, with 50.8% of them being male. The study emphasized risk variables such intravenous drug use (5.6%) and transfusions prior to HCV screening (14.3%). Hepatocellular carcinoma (HCC), liver cirrhosis, and chronic hepatitis were found in 69.5%, 18.9%, and 11.5% of patients, respectively. In 49.9% of cases, the levels of alanine aminotransferase were within the upper range of normal. The two most common genotypes were 1b (48.2%) and 2 (46.4%). Direct-acting antivirals (DAA) replaced interferon-based therapy in the 53.8% treatment rate overall. The untreated group was older, had a higher prevalence of HCC, and had lower levels of education than the treated group in the post-DAA-approval era. Out of the total cohort, 8.7% had various extra hepatic malignancies. Comorbidities included HBsAg positive (3.3%), diabetes (18.6%), cardiovascular disease (25.7%), mental disorders (4.2%), and cerebrovascular illnesses (1.8%) were also reported in the study (5).

CLINICAL SYMPTOMS OF HCV

Fatigue, vomiting, nausea, pain in the abdomen under the lower right ribs, pale stools, loss of appetite, mild fever, dark urine, arthritis, yellowish skin and eyes (jaundice), and a tickling sensation are the most frequently observed symptoms. The symptoms of HCV are classified into three phases:

The prodromal phase

Some patients experience sickness, including fever, joint pain, rashes, and angioneurotic edema, before the disease fully develops. These symptoms usually resolve before jaundice appears, which is the most common and distinctive symptom of HCV.

Pre-icteric phase

In this phase, the patient experiences respiratory issues and gastrointestinal disorders, which may include malaise, fatigue, muscle pain, nausea, and vomiting. These symptoms may be accompanied by weight loss, headache, nasal congestion, fever, pharyngitis, or cough. The pre-icteric phase lasts from 2-3 days to 2-3 weeks.

Icteric phase

During the icteric phase, patients may experience abdominal pain, uneasiness in the right upper quadrant, or diarrhea. They often notice a darkening of urine and light-colored stools. Loss of appetite, vomiting with a yellowish tint, scratching, and irritated skin lesions owing to intense itching are the most distinctive symptoms of hepatitis that appear during this phase (6-8).

DIAGNOSIS OF HCV

The initial diagnostic method for HCV infection involves serologic testing with Enzyme Immunoassays (EIAs), which identify antibodies against HCV C, NS3, NS4, and NS5 proteins [9]. Although EIAs have high specificity and sensitivity, they can occasionally produce false

positives [9, 10]. Therefore, positive serologic results need to be confirmed with HCV RNA testing to verify an active infection.[11].

HCV RNA testing is essential in cases with high clinical suspicion, utilizing methods such as reverse transcriptase-polymerase chain reaction (RT-PCR), transcription-mediated amplification (TMA), reverse transcription loop-mediated isothermal amplification (RT-LAMP), and branched DNA (bDNA) assays [12, 13]. These methods target highly preserved regions of the HCV genome, making them crucial for confirming chronic infection status and guiding treatment approaches.

Accurate staging of HCV-related liver disease, which historically depended on invasive liver biopsies, is crucial [14]. Although liver biopsies provide detailed insights, this invasive approach carries risks and limitations [15]. The move towards non-invasive methods, such as serum markers and sonographic elastography, is transforming HCV management [16-18]. These methods enable more frequent and less invasive monitoring, offering a clearer assessment of liver fibrosis without the drawbacks of traditional biopsy techniques [19].

TREATMENT OF HCV

The therapeutic approach for HCV infection has undergone a major transformation, especially with the advent of direct-acting antivirals (DAAs). This shift from interferon-based treatments to more effective and tolerable options has resulted in shorter treatment durations [20].

The introduction of DAAs marked a revolutionary step in HCV management, achieving cure rates above 95%. The new clinical benchmark, sustained virologic response (SVR), is defined as undetectable HCV RNA 12 weeks post-treatment (SVR12), instead of the previous 24 weeks [21, 22].

Therefore, the advent of Direct-Acting Antivirals (DAAs) transformed the treatment of chronic Hepatitis C Virus (HCV) infection, marking a crucial advance in the effort to manage and potentially eradicate the disease as a public health concern. In May 2011, the U.S. Food and Drug Administration (FDA) approved the first DAAs, telaprevir and boceprevir [23]. Subsequent approvals of additional DAAs represented a major therapeutic breakthrough, leading in a new era of hepatitis C treatment characterized by increased efficacy, improved tolerability, and shorter treatment durations [24].

Direct-Acting Antivirals (DAAs) specifically target certain steps in the Hepatitis C Virus (HCV) replication cycle. Clinical evidence strongly supports the effectiveness of DAA regimens, showing that over 95% of patients treated with DAAs achieve a sustained virological response (SVR), which is considered a virological cure [25-28].

Additionally, innovative therapeutic strategies are being explored to expand treatment options for HCV, particularly for challenging cases such as patients with hepatocellular carcinoma (HCC), as reviewed comprehensively by Medina et al. [29]. For instance, agents like ezetimibe, which target cellular cholesterol essential for viral entry, may offer a novel method to prevent HCV from entering hepatocytes [30].

HCV Vaccination Challenges

Despite the innovative impact of DAAs on HCV treatment, the pursuit of a preventive hepatitis C vaccine remains a critical public health priority [31]. While DAAs are highly effective, their high cost and distribution challenges limit accessibility, especially in low-income areas [32,33]. Moreover, curative treatments do not provide immunity against future infections, which is a significant concern for high-risk populations, such as injection drug users (IDUs) [34]. A vaccine would significantly reduce new infections and prevent HCV transmission within communities, offering a sustainable and cost-effective approach to combat the global HCV epidemic [35].

Promising vaccine strategies, such as the use of cyclic peptides that can elicit strong neutralizing antibody responses, face challenges in developing delivery systems to maximize their immunogenicity [36].

Recent advances in HCV vaccine research have shown encouraging results [37]. For instance, experimental work with DNA and peptide-based vaccines in murine models has made progress, including a significant development of a peptide vaccine derived from the HCV p7 protein [38]. Similarly, a DNA-based HCV vaccine has effectively elicited comprehensive T cell responses and memory, although it also triggered a non-neutralizing antibody response [39]. The potential of messenger RNA (mRNA) vaccine technology, which gained momentum during the COVID-19 pandemic, represents a promising area for HCV prevention research [40].

CONCLUSION

In conclusion, the clinical manifestations of HCV span three distinct phases, each with characteristic symptoms. Considerate these phases and their associated symptoms is crucial for the timely diagnosis and effective management of hepatitis C. While DAAs have transformed the treatment of hepatitis C, ongoing research into vaccine strategies, including cyclic peptides, DNA, and mRNA technologies, is essential to overcome current limitations such as high costs, accessibility issues, and a lack of immunity against reinfection. These innovative approaches hold promise for more effective and sustainable management of HCV, eventually reducing the global burden of the disease.

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