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Diagnostic Challenges of Hepatitis C

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A healthy woman in her 50s without diabetes or obesity presented for an annual physical examination. Her primary care physician recommended hepatitis C virus (HCV) testing because she was born between 1945 and 1965, screening parameters based on recommendations from the Centers for Disease Control and Prevention (CDC) and the US Preventive Services Task Force (USPSTF).^{1,2} The patient's hepatitis C antibody (anti-HCV) result was positive. Additional tests performed to evaluate the extent of liver disease were unremarkable: alanine aminotransferase of 34 U/L (reference range, 7–35), aspartate aminotransferase of 28 U/L (reference range, 8–30), total bilirubin of 0.4 mg/dL (reference range, 0.2–1.2), alkaline phosphatase of 95 IU/L (reference range, 30–130), and albumin of 4.0 g/dL (reference range, 3.0–4.5). She had a hemoglobin level of 14.5 g/dL (reference range, 12–16), white blood cell count of $7.1 \times 10^9/L$ (reference range, 4–10), platelet count of $210 \times 10^9/L$ (reference range, 150–400), and INR of 1.0. A baseline abdominal ultrasound to look for features of cirrhosis showed mild increased echogenicity of the liver. The liver was not nodular and the spleen not enlarged. The patient was asymptomatic. Other laboratory values are shown in the Table.

Answer

D. This patient is infected with the most common strain of HCV in the United States and it has lower response rates to interferon-based therapy.

Test Characteristics

Enzyme immunoassays for anti-HCV are used to screen for HCV infection. These assays are very specific (>99%) and sensitive (>97%).³ However, false-positives can occur when testing low-prevalence (<10%) populations (positive predictive value, 89%–91%).^{3–6} False-negatives can occur in patients with immunosuppression.³ Any positive anti-HCV result should be followed by an HCV RNA test to determine whether there is ongoing infection.^{3,4} HCV RNA levels may also be obtained to monitor treatment response.³ There is no role for monitoring HCV RNA viral load outside the context of antiviral therapy. Quantitative HCV

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RNA tests are sensitive (96%–98% with lower limit of detection of 10–15 IU/mL) and specific (98%–99%).^{3,6} HCV genotyping should be pursued in any patient in whom treatment is considered because it guides therapeutic selection.^{3,7} The host genetic marker IL-28B is associated with greater likelihood of response to interferon and ribavirin, but there is little or no association with response to recently approved direct-acting antiviral agents.⁸

The Medicare midpoint reimbursement is \$26.51 for an anti-HCV test, \$79.52 for an HCV RNA test, and \$478.21 for HCV genotyping.⁹

Application of Test Result to This Patient

A positive anti-HCV and HCV RNA result indicates chronic HCV infection.³ An HCV genotype was obtained to guide treatment decisions and choice of therapy.^{3,7} Genotype 1 is most common in the United States, representing 75% of strains. Of 2 subtypes (1a and 1b), 1a is more common.^{3,7} Genotype 1 is associated with a lower rate of sustained virologic response to pegylated interferon and ribavirin.⁷ Two new direct-acting antiviral agents—simeprevir (a protease inhibitor) and sofosbuvir (a nucleotide polymerase inhibitor)—were approved for HCV treatment in 2013. Adding these agents to pegylated interferon and ribavirin results in improved treatment efficacy with shorter treatment duration.^{8,10}

For this patient, results of the laboratory and ultrasound testing suggest that cirrhosis is unlikely. Given the absence of cirrhosis, no prior hepatitis therapy, and HCV genotype 1a, this patient's expected rate of sustained virologic response after 12 weeks of sofosbuvir, pegylated interferon, and ribavirin is 92%.

In summary, this patient has chronic HCV infection with a high viral load, making answers A and B incorrect. Normal aminotransferase levels on a single occasion are insufficient to exclude the presence of liver damage (answer C).

What Are Alternative Diagnostic Testing Approaches?

The CDC and USPSTF recommend that any baby boomer born between 1945 and 1965 should undergo one-time screening for HCV even without evidence of other risk factors or clinical findings of liver disease. This is because US residents born between 1945 and 1965 have a 5-fold higher prevalence of HCV than other age groups.^{1,2} Patients with HCV should be screened for hepatitis B and HIV because these viruses have similar risk factors.

Approximately 170 million persons worldwide have chronic HCV infection.^{1–3} Twenty percent of chronically infected patients develop cirrhosis. Early treatment of chronic HCV can reduce the morbidity and mortality associated with HCV. As the efficacy of HCV treatment improves and sustained virologic response rates of 90% or higher are achieved with short (12 weeks) courses of interferon-free regimens, most HCV patients should be considered treatment candidates.

Patient Outcome

Because this patient did not have evidence of cirrhosis, she was advised that deferring treatment until interferon-free regimens are approved in the next 1 to 2 years would be

appropriate. However, the patient selected treatment with sofosbuvir, pegylated interferon, and ribavirin because she did not want to wait for treatment and did not have medical or psychological conditions that would decrease her tolerance to pegylated interferon.

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HOW DO YOU INTERPRET THESE TEST RESULTS?

- A.** This patient has a low viral load.
- B.** This patient has antibody to HCV and is no longer infected.
- C.** This patient has no liver damage because her aminotransferase levels are not elevated.
- D.** This patient is infected with the most common strain of HCV in the United States and it has lower response rates to interferon-based therapy.

Clinical Bottom Line: Hepatitis C Virus Testing

- Any patient with known risk factors for HCV or born between 1945 and 1965 should be screened for HCV.^{1,2}
- Enzyme immunoassays for anti-HCV are used to screen for HCV infection and are very sensitive and specific.
- Any patient with a positive anti-HCV should have an HCV RNA tested to determine whether there is ongoing infection.
- An HCV genotype should be tested in any patient in whom treatment is being considered, to guide treatment decisions and predict treatment responses.
- Recently approved therapies achieve improved sustained virologic response rates with shorter therapy duration and fewer adverse reactions.

Table

Laboratory Values for Hepatitis and HIV

Laboratory Test	Value	Reference Range
Hepatitis C virus RNA	1 764 200 IU/mL	Not detected
Hepatitis C virus genotype	1a	Not applicable
Hepatitis B surface antigen	Negative	Negative
Anti-HIV	Negative	Negative