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Educational Case: Hepatitis B Virus

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

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Primary Objective

Objective M3.1: Hepatotropic Viruses: Describe the laboratory findings that diagnose hepatitis and correlate with the different possible clinical outcomes for each of the major hepatotropic viruses.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic M: Microbiology; Learning Goal 3: Virology.

Patient Presentation

A 28-year-old female presents to the clinic with a 10-day history of flu-like symptoms, including anorexia and malaise. She does not report any pertinent prior medical history or surgeries. She takes no medications. Her family history is noncontributory, and she reports no sick contacts. She is sexually active with multiple partners and has used oral contraceptives regularly for the past 12 years. She has not traveled outside the United States in the past 5 years.

On physical examination, she is alert and oriented, in no acute distress. Her vital signs are temperature of 99.9°F, pulse 78/minute, respirations of 18/minute, and blood pressure of 121/78 mm Hg. Her extraocular muscles are intact; however, mild scleral icterus is noted. Heart sounds are regular rate and rhythm without murmurs, and lungs are clear to auscultation bilaterally. The abdomen is soft and nontender, except the liver is tender when palpated and extends 8 cm below the costal margin, with a smooth edge. Initial laboratory testing is performed and shown in Table 1.[1]

Diagnostic Findings, Part I

Complete blood count (CBC) and basic metabolic panel (BMP) are within normal limits. Liver function tests are performed, and the findings are reported in Table 1.

Questions/Discussion Points, Part I

Given the Clinical History, What Is a Broad Differential Diagnosis?

The differential diagnosis for a patient with flu-like symptoms, an enlarged liver, and scleral icterus is broad and includes hemolytic anemia, hepatotropic viruses,[2] and other sources of

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Table 1. Initial Laboratory Findings.[1]

Alanine aminotransferase (ALT)	3817 U/L	7-55 U/L
Aspartate aminotransferase (AST)	2152 U/L	8-48 U/L
Alkaline phosphatase (ALP)	176 U/L	45-115 U/L
Albumin	3.4 g/dL	3.5-5 g/dL
Total protein	6.7 g/dL	6.3-7.9 g/dL
Total bilirubin	8.5 mg/dL	0.1-1.2 g/dL

liver injury such as autoimmune disorders including Sjögren disease and primary sclerosing cholangitis, drug induced (eg, acetaminophen), and chronic alcohol abuse. HIV must also be considered. The history and viral serology studies will help to narrow this differential.[3]

How Does the Initial Hepatic Panel Help Narrow the Differential Diagnosis?

The initial hepatic panel shows very elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT), while the alkaline phosphatase is relatively normal. A low albumin may indicate liver dysfunction (impaired synthesis); however, this patient's albumin is only slightly low. Elevated total bilirubin may indicate hemolysis or liver dysfunction (impaired metabolism of bilirubin). When AST and ALT are highly elevated, particularly when disproportionately elevated compared to alkaline phosphatase, acute hepatitis must be strongly considered in the differential diagnosis. Classically, AST is significantly higher than ALT in the setting of alcoholic hepatitis. These patients will also likely have a history of chronic alcohol use. When ALT is higher than AST, viral hepatitis is favored. A thorough history and assessment of risk factors can help to determine which of the viral hepatitis types is most likely involved.[3]

What Is the Most Likely Diagnosis?

Given the patient's presentation of flu-like symptoms with jaundice and tender hepatomegaly, acute viral hepatitis must be considered very high on the differential diagnosis. Her history of multiple sexual contacts without barrier protection is a risk factor for hepatitis B in particular, as well as HIV. As indicated in Table 1, the CBC is normal, ruling out anemia, and the BMP is also within normal limits. The diagnosis can be confirmed with viral serology. Viral serology is ordered.

Diagnostic Findings, Part II

Viral serology can be very helpful to narrow the differential diagnosis. Viral serology results are reported in Table 2.

Questions/Discussion Points, Part II

How Does the Hepatitis Serology Help Narrow the Differential Diagnosis?

As seen in Table 2, the serology is positive for hepatitis B.

Table 2. Viral Serology for Hepatitis B.

HBsAg	Positive
HBeAg	Positive
IgM Anti-HBc	Positive
IgG Anti-HBe	Negative
IgG Anti-HBs	Negative
HBV-DNA	Positive

Abbreviations: HBc, hepatitis B core; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; Ig, immunoglobulin.

What Are the Risk Factors for Hepatitis B Compared to Other Types of Viral Hepatitis?

Hepatitis B is most often transmitted by bodily fluids (blood or semen), via unprotected sexual contact or contaminated needles as in intravenous drug use, or very rarely via blood products. Though rare in the United States, vertical transmission (from mother to child during childbirth) is more common in Asian countries where the prevalence of chronic hepatitis B is higher among the general population. Hepatitis A is more commonly seen with ingestion of infected foods, such as raw oysters or other shellfish, and spreads through fecal–oral contact; it is endemic in developing countries with poor hygienic conditions. Hepatitis C is most commonly transmitted via blood and through contaminated needles in the setting of intravenous drug use, tattoos, or piercings. Hepatitis D is almost exclusively seen as a coinfection with hepatitis B. Hepatitis E is transmitted via the fecal–oral route, and the presentation may be severe in pregnant women.[2]

Diagnostic Findings, Part III

The patient's disease state—active infection versus cleared/immunized, acute versus chronic—can be better characterized using viral serum markers, as given in Table 3.

Questions Discussion, Part III

What Are the Possible Clinical Outcomes of Hepatitis B?

Once exposed, a patient may experience an acute, symptomatic viral hepatitis accompanied by an immune response. A healthy, immunocompetent patient will likely be able to clear the infection (and become subsequently immune), whereas other patients, particularly if they are immunocompromised, are unable to completely clear the acute infection. These patients will either progress rapidly to liver failure (fulminant hepatitis) or slowly to possible cirrhosis (chronic hepatitis). It is also possible for a patient to experience a subclinical hepatitis after exposure and progress to chronic disease without ever manifesting acute hepatitis.[2]

Chronic hepatitis B also carries increased risk of developing hepatocellular carcinoma, even before progressing to end-stage cirrhosis. Known patients with chronic hepatitis B from high risk populations should be monitored for this complication via a combination of liver ultrasound and α-fetoprotein levels.[2,4]

Table 3. Viral Serology Interpretation for Hepatitis B.[2]

Marker	Definition	Significance
HBsAg	Surface antigen	Active infection
HBeAg	E-antigen (replication marker)	Active infection
IgM Anti-HBc	Antibody against core antigen	Acute infection
IgG Anti-HBe	Antibody against E-antigen	Prior exposure—cleared or chronic infection
IgG Anti-HBs	Antibody against surface antigen	Prior exposure—cleared or chronic infection History of vaccination (if isolated finding)
HBV-DNA	Viral DNA	Active infection

Abbreviations: HBc; hepatitis B core; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; Ig, immunoglobulin.

What Are Possible Treatments of Hepatitis B?

Acute hepatitis B requires only supportive treatment while the patient clears the infection.[3] Antiviral medications have not been shown to shorten or improve the course for patients with acute hepatitis with severe presentations. Patients with chronic hepatitis B should be treated with interferons and antivirals and regularly tested for viral loads and liver function markers to monitor for progression (increasing viral load and/or declining liver function).[3]

What Are the Typical Clinical Findings and Clinical Course of the Other Types of Hepatitis Infection (A, C, D, and E)?

Hepatitis A presents as acute hepatitis, often without jaundice. The infection usually resolves within 2 months following the acute illness, with rare progression to fulminant hepatitis. Hepatitis C will become chronic in about 80% to 90% of infected patients, some of whom may never manifest an acute hepatitis. These patients are at risk for eventual cirrhosis and hepatocellular carcinoma (rarely without preexisting cirrhosis). Hepatitis D is only able to replicate in the presence of hepatitis B. It presents as an unusually severe hepatitis B infection (acute coinfection with both B and D) or an exacerbation of a preexisting chronic hepatitis B infection (superinfection with hepatitis D). Hepatitis E typically presents like an acute hepatitis, but pregnant patients may experience a severe course with increased risk of fulminant hepatitis and death.[2]

Are All the Hepatitis Viruses the Same?

Hepatitis viruses are linked because they all invade hepatocytes. However, they actually come from different virus families and have varying characteristics. Hepatitis A is single-stranded RNA picornavirus. Hepatitis B virus is an enveloped hepadnavirus with partially double-stranded, circular DNA. Hepatitis C is a single-stranded RNA flavivirus. Hepatitis D is a defective circular single-stranded RNA deltavirus that can only replicate in the presence of hepatitis B or as a superinfection with chronic hepatitis B. Hepatitis E is an enterically transmitted single-stranded RNA calicivirus.[2]

Teaching Points

- Patient presentation and history can help differentiate among the viral hepatitis etiologies. Suspect hepatitis B in patients presenting with acute hepatitis (flu-like symptoms and jaundice), particularly with a history of either unprotected sexual contact or intravenous drug use.[2]
- Hepatitis A is transmitted fecal–orally and typically presents with acute hepatitis. Progression to fulminant hepatitis is rare and supportive care is indicated.[2]
- Hepatitis C is transmitted via contaminated needles, as in intravenous drug use, tattoos, or piercings. The course is typically chronic, and patients are at risk of developing cirrhosis and hepatocellular carcinoma.[2]
- Hepatitis D is unable to replicate unless in the presence of hepatitis B, and so only presents as either a coinfection (severe initial course) or a superinfection in a patient with known chronic hepatitis B (sudden exacerbation).[2]
- Hepatitis E is fecal–orally transmitted and presents as acute hepatitis. Pregnant patients are at increased risk for a severe course, including fulminant hepatitis and death.[2]
- Diagnosis can be made with viral serologies. It is important to characterize the infection as acute or chronic to determine the appropriate treatment course.[2]
- Infected patients presenting with acute hepatitis B will either clear the infection and recover or progress to either acute liver failure or chronic hepatitis and eventual cirrhosis. Patients may also skip the acute viral illness stage and present much later with a subclinical chronic infection.[2]
- Patients with chronic hepatitis B are at increased risk for developing hepatocellular carcinoma, even before reaching end-stage cirrhosis.[2]
- Acute hepatitis B is treated with supportive care. Chronic hepatitis B infection will likely require long-term treatment with interferons and antivirals.[4]

Authors' Note

The views expressed in this case are those of the author(s) and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or US Government.

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