GI DISEASE WORKSHOP

CASE STUDIES

ANSWERS TO QUESTIONS

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CASE #1

Application

- 49 year old man, non-smoker
- Senior vice president of a software manufacturer
- Applying for $750,000 (US$) with waiver of premium

Insurance exam

- 5'10", 205 lbs. (178 cm, 93.1 kg)
- BP 132/80 Pulse 64
- Family history: father died of a heart attack at age 72
- Total cholesterol 190 mg/dl (4.91 mmol/L), HDL 42 mg/dl (1.09 mmol/L)
- Glucose normal
- ALT elevated at 81 U/L (1.8 x normal), GGT and AST normal
- No reflex testing performed
- Urinalysis: within normal limits; negative for cotinine/nicotine

Medical history

- Records dated back to 2008. Had been followed for "white coat hypertension" and "borderline cholesterol". Told to exercise more and watch his diet – not put on any medications.
- Suffered a myocardial infarction in 2009
- Prior liver tests were normal
- Total cholesterol 256 mg/dl (6.62 mmol/L), HDL 44 mg/dl (1.14 mmol/L)
- He was begun on atorvastatin, atenolol and aspirin.
- No symptoms since MI.

Questions

1. What is the likely cause(s) of the ALT elevation? **Most likely fatty liver in light of lipid levels. A drug reaction is a possibility but difficult to prove.**
2. Would reflex testing with an alcohol marker or hepatitis studies likely be helpful? Which would be more helpful? **Neither reflex test is likely to be particularly helpful as the positive rate with an isolated ALT elevation is in the 2%-3% range at most.**
3. How would you assess the mortality risk relative to the elevated ALT? **The mortality risk associated with a mildly elevated ALT level is minimal to none.**
4. Would a normal reflex test(s) affect your mortality assessment? **With the very low positive rates for the reflex tests, their results are unlikely to change the mortality assessment.**

Alternate Scenario

- GGT elevated at 117 U/L (1.8 x normal), ALT and AST normal

- Other details are the same

Questions

1. What is the likely cause(s) of the GGT elevation? **Again likely fatty liver.**
2. Would reflex testing with an alcohol marker or hepatitis studies likely be helpful? Which would be more helpful? **Neither is likely to be helpful with the low positive rates for both.**
3. How would you assess the mortality risk related to the elevated GGT? **Mildly increased risk, likely higher than ALT alone.**
4. Would the risk increase if the GGT was 3 times normal (195 U/L)? **The mortality risk associated with GGT appears to increase with increasing degrees of elevation.**
5. Would the probability of a positive alcohol marker change? **The rate of positive alcohol markers does not increase substantially with higher GGT elevations. The likelihood of a positive alcohol marker does not grade up as the level of GGT rises.**
6. Would the risk change if the HDL was 72 mg/dl (1.86 mmol/L) **The rate of positive alcohol markers increases significantly (about 5 times) when an elevated GGT is associated with a high HDL level.**
7. Would a normal alcohol marker reduce the mortality risk? **The benefit of the negative marker would be greater when the risk of alcohol abuse/presence of a positive alcohol marker is greater i.e. with the combination of an elevated HDL and GGT as opposed to an elevated GGT alone.**

Alternate Scenario

- ALT is elevated at 117 U/L (2.6 times normal) and AST is elevated at 59 U/L (1.8 times normal), GGT is normal
- Other details are the same

Questions

1. What is the likely cause(s) of the elevations? **The cause is more likely related to hepatitis with this pattern of enzyme elevation.**
2. Would reflex testing with an alcohol marker or hepatitis studies likely be helpful? Which would be more helpful? **Markers for hepatitis B surface antigen and hepatitis C antibody would be more helpful in ruling out a major potential pathologic cause for the elevations. In some scenarios (an associated elevation of the HDL level, an AST:ALT ratio) an alcohol marker would be more helpful.**
3. How would you assess the mortality risk related to the abnormal liver tests? **The mortality risk would be moderately increased.**
4. Would the risk change if the AST was 117 U/L (3.5 times normal) and ALT was 59 U/L (1.3 times normal)? Why? **An AST:ALT ratio > 1 is associated with a higher risk of alcohol abuse or a higher risk of fibrosis/cirrhosis if the cause of the elevations is not related to alcohol. The mortality risk increases significantly.**

5. Would the probability of a positive alcohol marker change? **The risk of a positive alcohol marker would increase significantly with an AST:ALT ratio >1.**

Alternate Scenario

- GGT is elevated at 228 U/L (3.5 times normal), ALT is elevated at 130 U/L (2.9 times normal) and AST is elevated at 75 U/L (2.3 times normal)

Questions

1. What is the likely cause(s) of the elevations? **Most likely related to hepatitis but alcohol is a strong possibility in some scenarios.**
2. Would reflex testing with an alcohol marker or hepatitis studies likely be helpful? Which would be more helpful? **The hepatitis tests would be more helpful unless the HDL level is elevated.**
3. How would you assess the mortality risk related to the abnormal liver tests? **The mortality risk would be moderate to high.**
4. Would your assessment change with any of the following additional scenarios?
    a. Build is now 5'10", 300 lbs. (178 cm, 136.4 kg) **Yes, higher, risk of steatohepatitis is increased.**
    b. Alkaline phosphatase is 265 U/L (2.12 times normal) **Yes, higher, mortality risk is increased significantly.**
    c. Bilirubin is 2.8 mg/dl (47.9 umol/L) **Yes, higher, concern for impaired synthetic function is increased.**
    d. Serum albumin 3.3 mg/dl (33 g/L) **Yes, higher, concern for impaired synthetic function is increased.**
    e. Applicant sees a gastroenterologist who orders an anti-smooth muscle antibody, anti-mitochondrial antibody, ceruloplasmin level, anti-nuclear antibody (ANA), serum ferritin, iron saturation, alpha 1-antitrypsin level, all of which are normal. **Yes, lower, multiple other possible causes for significant liver disease beyond the usual problems (fatty liver, alcohol, hepatitis) have been eliminated as a cause or rendered less likely (autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, Wilson's disease, alpha 1-antitrypsin deficiency)**

CASE #2

Application

- 38 year old woman, current smoker
- Born and raised in Taiwan, lives in the United States
- Homemaker
- Applicant denies alcohol use
- Applying for $1 million (US$) survivor policy

Insurance exam

- 5'5", 145 lbs. (165 cm, 65.9 kg)
- BP 142/84, pulse 70
- Family history: father died of hepatocellular cancer at age 60; mother had a heart attack at 62 and died of heart failure at age 71. Brother has cirrhosis; other brother and a sister in good health.
- Total cholesterol 198 (5.12 mmol/L), HDL 50 (1.29 mmol/L)
- ALT elevated at 122 U/L (2.7 times normal), AST elevated at 77 U/L (2.3 times normal), GGT, alkaline phosphatase and bilirubin are normal
- Hepatitis B surface antigen is positive, hepatitis B core antibody (total) is positive, hepatitis B surface antibody is negative, hepatitis B e antigen is positive
- Urinalysis: within normal limits; positive for cotinine/nicotine

Medical history

- Applicant was diagnosed with hepatitis B in 1995.
- Her liver enzymes were initially normal but have been elevated since at least 3 years ago.
- She was treated with interferon in 2009 but did not tolerate the therapy.
- Her last viral DNA level was 550,000 IU/ml
- The viral genotype was C

Questions

1. How would you assess the mortality risk? **The mortality risk is high.**
2. What are the key prognostic factors? **The adverse prognostic factors here are the positive hepatitis B e antigen, the worsening LFT levels, the high viral DNA level, the presence of genotype C, the positive smoking history, the strong family history of hepatocellular cancer/cirrhosis.**
3. Are there other test results that you would be interested in? **If you were considering making an offer of insurance it would be good to know that screening tests for hepatocellular cancer such as the alfa fetoprotein and a liver ultrasound were normal.**
4. Would the mortality risk change if this were man instead woman? **The risk would be higher in a male (risk is increased 3-4 times).**
5. Would the mortality risk change if the e antigen was negative and the viral DNA level was still elevated at 550,000 IU/ml? **The risk would be about the same.**

The high DNA level suggests very active viral replication. One would question the presence of a pre-core mutant.

6. How would the presence of a Basal Core Promoter mutation affect the risk? **This mutation increases the risk of hepatocellular cancer and cirrhosis.**

Alternate Scenario

- Applicant is a known hepatitis B carrier since 1995
- ALT and AST have been consistently normal
- Viral DNA levels have been followed regularly, most recent level was 6750 IU/ml
- Regular follow up with alpha fetoprotein has been normal as has regular ultrasound examinations of the liver
- Hepatitis B surface antigen is positive, hepatitis B core antibody (total) is positive, hepatitis B surface antibody is negative, hepatitis B e antigen is negative, hepatitis B e antibody is positive

Questions

1. What are the key prognostic factors? **ALT and AST have been normal for a long time, viral DNA level is relatively low but can still be detected, the e antigen is negative, regular follow up for hepatocellular cancer has been normal.**
2. Is there a risk of reversion to hepatitis e antigen positive status? **There is an ongoing risk of reversion to an e antigen positive status. If there is a reversion to an e antigen positive status, there is usually a flare of clinical hepatitis.**
3. If the applicant was found to have the Pre Core mutation how would it affect the mortality risk? **The risk of hepatocellular cancer and cirrhosis would likely not be increased.**
4. How would you assess the mortality risk? **The mortality risk is mildly increased.**

Alternate Scenario

- Applicant was diagnosed with hepatitis B in June, 2010
- ALT and AST were initially elevated at 2-3 times normal
- Applicant was started on entecavir (Baraclude) in December, 2010 and has continued to take the medication
- Viral DNA levels became undetectable after starting therapy and have remained undetectable.
- Regular follow up with alpha fetoprotein has been normal as has regular ultrasound examinations of the liver

Questions

1. Is there any risk of relapse of viral DNA levels? **The viral DNA levels may increase again, especially if the medication is discontinued.**

2. What if the entecavir was discontinued and the DNA levels remained undetectable? **The likelihood of relapse is low and gets lower the longer the duration of undetectable viral DNA levels.**
3. Is there any risk of hepatocellular cancer if the DNA level remains undetectable? **There remains an increased risk of hepatocellular cancer compared to the general population. The relative risk is about 4 times relative to the general population. However, because the risk of hepatocellular cancer is very low in the population, the absolute risk is low and the overall mortality of a group of individuals with this pattern is not substantially increased.**
4. How would you assess the mortality risk? **The risk would be mildly increased at this point. If the DNA remained undetectable after the cessation of the oral medication the excess risk would be minimal to none but because of the ongoing hepatocellular cancer risk probably not better than that of the usual insurance buying population.**

CASE #3

Application

- 48 year old man
- House painter
- Applying for $100,000 (US$) term

Insurance exam

- 6', 225 lbs. (183 cm, 102.3 kg)
- BP 150/90, pulse 60
- ALT is mildly elevated at 68 U/L (1.51 times normal), AST, GGT are normal
- Total cholesterol 190 mg/dl (4.91 mmol/L), HDL 40 mg/dl (1.03 mmol/L)
- He admits to drinking 2-3 beers per day
- CDT alcohol marker is normal
- Hepatitis B surface antigen is negative
- Hepatitis C enzyme immunoassay (EIA) is positive
- Urinalysis: normal, positive for cotinine/nicotine

Medical history

- Applicant has no history of blood transfusions
- His medical records indicate mild elevations of the ALT levels in the past that were never formally evaluated
- He did have an abdominal ultrasound in November, 2010 for abdominal pain that showed increased internal echoes suggestive of fatty liver, the test was otherwise normal with no gallbladder, pancreas, or other liver pathology
- He has had no further GI symptoms

Questions

1. How would you assess the likely cause for the elevated ALT? **The most likely cause of the elevated ALT is chronic hepatitis C.**
2. Would you require additional testing to diagnose a hepatitis C infection? **Some clinicians would confirm a positive hepatitis C EIA with a recombinant immunoblot assay (RIBA). Some but not all U.S. insurance laboratories routinely perform the RIBA assay on all positive EIA tests. The conservative position would be to assume an active hepatitis C infection until proven otherwise.**
3. What are the other options for additional testing if you chose to pursue that option? **The other testing options are a RIBA assay or hepatitis C virus RNA assay. The RIBA assay may have limited availability in the future.**
4. If he has hepatitis C what is the most likely cause and when did the infection likely occur? **The most likely cause is IV drug abuse, often done transiently in younger ages. Sexual transmission is possible but not likely.**
5. What factors in the case would influence the prognosis? **The regular alcohol use and the possible steatosis would be adverse prognostic factors for progression and increased mortality.**

6. How would you assess the mortality risk? **The mortality risk, with the alcohol use and steatosis in this case, is high. Without these adverse prognostic factors the risk would be more moderate to high (2.5-3.0 relative mortality).**
7. If this were a 25 year old woman instead of a 48 year old man, would the mortality risk be more, less or the same? **The risk is lower in women.**
8. If he had a liver biopsy in the last 6 months that showed moderate portal inflammation and moderate portal fibrosis with early bridging fibrosis would it change your assessment? **No, that is about what you would expect based on the clinical course and adverse prognostic factors.**
9. What if the biopsy in the same time frame showed mild inflammation and minimal fibrosis? **The risk would be lower because it would indicate only minimal progression despite the long course and adverse factors, thus, a pace slower than what would be expected.**

Alternate Scenario

- Applicant was diagnosed with hepatitis C in June, 2010
- He does not drink alcohol
- ALT has been mildly elevated at 1.5 to 2 times normal
- His infection is with genotype 1b
- His viral RNA level was measured and found to be 1.4 million IU/ml

Questions

1. Does the ALT level influence the prognosis? **No, ALT levels are usually only mildly elevated, frequently vary over time, often dropping into the normal range and do not correlate with prognosis.**
2. Does the viral genotype influence the prognosis? **The viral genotype does not influence prognosis but it does predict response to therapy. The response to therapy is lower with genotype 1b.**
3. Does the viral RNA level influence the prognosis? **The viral RNA level is not associated with prognosis.**

Alternate Scenario

- He is started on therapy with PEG interferon and ribavirin (Copegus, Rebetol)
- His viral RNA drops to undetectable levels by 12 weeks of therapy
- His treatment is stopped at 48 weeks and the viral levels are still undetectable at that time
- At a 3 month follow-up visit his viral load has elevated to 800,000 IU/ml
- After a period of 6 months he is retreated with the same medications with the addition of telaprevir (Incivek)
- His viral RNA load again drops to undetectable levels and remains there until the completion of the course of therapy
- At a follow up visit 24 weeks after completion of therapy the RNA levels are still undetectable (sustained viral response)

Questions

1. Does the viral genotype influence response rate? **Yes, the response rate varies with genotype. Response rates to therapy are generally better with genotypes 2 and 3.**
2. Is there a difference in prognosis between non-response (no reduction of viral RNA to undetectable levels) and relapse (rebound of RNA values to detectable levels after an initial response)? **Yes, individuals who relapse have a prognosis better than non-responders but not as favorable as those who remain in remission.**
3. Does the addition of a protease inhibitor like telaprevir or boceprevir influence response rates in genotype 1? **Yes, response rates are significantly better.**
4. What is the probability of relapse after achieving a sustained viral response (SVR) **The probability of a relapse after a SVR i.e. undetectable viral levels 24 weeks after completion of therapy, is less than 1%.**
5. How would you assess the mortality risk with a relapse, SVR? **The mortality risk is mild to moderate for a relapse and minimal to none for an SVR with no complications.**