GI DISEASE WORKSHOP

CASE STUDIES

(ANSWER VERSION)

American Academy of Insurance Medicine
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CASE #1

Application

- 52 year old female, non-smoker, born in the US
- Vice president of a marketing firm
- Applying for $1, 000,000 (US$) with waiver of premium

Insurance exam

- 5'3", 165 lbs. (160 cm, 75 kg), BMI 29.2
- BP 128/80 Pulse 68
- Family history: father died of prostate cancer at age 75
- Total cholesterol 182 mg/dl (4.71 mmol/L), HDL 48 mg/dl (1.24 mmol/L)
- Glucose normal
- ALT elevated at 75 U/L (1.7 x normal), GGT and AST normal
- No reflex testing performed
- Urinalysis: within normal limits; negative for cotinine/nicotine

Medical history

- Records dated back to 2015. She had been followed for "prehypertension" and "borderline cholesterol".
- Told to exercise more and watch her diet – initially not put on any medications.
- Prior liver tests were normal
- Total cholesterol 256 mg/dl (6.62 mmol/L), HDL 44 mg/dl (1.14 mmol/L)
- She was begun on atorvastatin in 2018
- She has remained asymptomatic

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 in a US insurance applicant population 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.**

5. Would the assessment change if the applicant had entered the US from Korea 10 years ago? **The mortality risk is higher in individuals who have immigrated from Asia, likely because of the higher prevalence of hepatitis B.**
6. Would the risk change in the original case if the ALT was low normal at 8 U/L? **Yes, the mortality risk is higher in individuals with a low normal (< 10 U/L) ALT and AST. The presumed etiology is sarcopenia or reduced muscle mass.**

Alternate Scenario

- GGT elevated at 75 U/L (1.7 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. Other possibilities include alcohol use and drug induction of the enzyme.**
2. Would reflex testing with an alcohol marker or hepatitis studies likely be helpful? Which would be more helpful? **None is likely to be helpful with the low positive rates for the reflex tests.**
3. How would you assess the mortality risk related to the elevated GGT? **Mildly increased risk, higher than ALT alone. The increased risk is primarily due to cardiovascular disease but cancer may play a part as well.**
4. Would the risk increase if the GGT was 3 times normal (135 U/L)? **The mortality risk associated with GGT increases with increasing degrees of elevation of the enzyme.**
5. Would the probability of a positive alcohol marker change with this higher elevation? **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 90 mg/dl (2.33 mmol/L) **The probability of a positive alcohol marker increases significantly (about 4-5 times) when an elevated GGT is associated with a high HDL level. Interestingly, the mortality does not increase substantially despite the higher rate for CDT positivity when only the GGT is elevated. The reason for the lack of change in mortality is not clear but may be due to the protective value of HDL on cardiovascular mortality.**
7. Would a normal alcohol marker reduce the mortality risk? **Since the mortality related to the isolated GGT is not changed markedly by the elevated HDL level, the risk would likely not be substantially altered by a negative CDT.**
8. Is there any risk with a GGT at the very low end of the normal range? **Unlike with ALT and AST, a low normal GGT is not associated with increased mortality.**

Alternate Scenario

- ALT is elevated at 126 U/L (2.8 times normal) and AST is elevated at 53 U/L (1.6 times normal), GGT is normal
- Other details are the same

Questions

- What is the likely cause(s) of the elevations? **Hepatitis is the most likely cause with this pattern of enzyme elevation. Fatty liver is a possibility with this pattern as well**
- 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 > 1) an alcohol marker would be more helpful.**
- How would you assess the mortality risk related to the abnormal liver tests? **The mortality risk is mildly increased with this level of elevation.**
- Would the risk change if the AST was 109 U/L (3.3 times normal) and ALT was 72 U/L (1.6 times normal)? If so, why? **An AST:ALT ratio > 1 is associated with a higher risk of alcohol abuse or a higher risk of fibrosis/cirrhosis even if the cause of the elevations is not related to alcohol. Some recent studies suggest that the risk of cardiovascular disease is increased as well. The mortality risk increases significantly with the altered ratio.**

  Would the probability of a positive alcohol marker change? **The probability of positive alcohol marker would increase significantly.**

Alternate Scenario

- GGT is elevated at 158 U/L (3.5 times normal), ALT is elevated at 108 U/L (2.4 times normal) and AST is elevated at 75 U/L (2.5 times normal)

Questions

1. What is the likely cause(s) of the elevations? **Most likely related to hepatitis or fatty liver with this ALT:AST ratio 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 5'8", 270 lbs. (173 cm, 122.7 kg) **Risk is still moderate to high but cause might be different. In this scenario the risk of steatohepatitis and possible secondary cirrhosis is increased significantly.**
    b. Alkaline phosphatase is 255 U/L (2.04 times normal) **Yes, higher, mortality risk is increased significantly.**
    c. Bilirubin is 2.8 mg/dl (42.8 umol/L) **Yes, higher, concern for impaired synthetic function is increased. However, a benign cause for elevated bilirubin such as Gilbert's syndrome is possible with this relatively low level.**
    d. Serum albumin 3.2 mg/dl (32 g/L) **Yes, higher, concern for impaired liver synthetic function is increased substantially.**
    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 2009.
- Her liver enzymes were initially normal but have been elevated since at least 3 years ago.
- She was treated with interferon in 2015 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 (hepatocellular cancer 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 which inhibits the production of the e antigen.**
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 2018
- 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 increases with some variants. The risk of cirrhosis would likely not be increased.**
4. How would you assess the mortality risk? **The mortality risk is mildly increased with the still detectable viral load.**

Alternate Scenario

- Applicant was diagnosed with hepatitis B in June, 2020
- ALT and AST were initially elevated at 2-3 times normal
- Applicant was started on entecavir (Baraclude) in December, 2020 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? Would there be any risk of hepatocellular cancer if the hepatitis B surface antibody became positive? **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 US population, the absolute risk is low and the overall mortality of a group of individuals with this pattern is not substantially increased. Even after the development of the hepatitis B surface antibody the risk of hepatocellular cancer would still be increased because the viral cccDNA becomes integrated in the nucleus of the hepatocytes.**
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.**