GI DISEASE WORKSHOP

CASE STUDIES

(ANSWER VERSION)

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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. 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 (195 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? **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 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.

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 mildly 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
- 40 year old male, non-smoker
- Occupation – insurance agent
- Applicant admits to social alcohol use
- Applying for 3 million (US$)

Insurance exam
- BMI 27
- BP 132/78, pulse 64
- Family history: father died from “bone cancer” age 69, mother alive with HTN only, no siblings.
- Total cholesterol 225 (5.82 mmol/L), HDL 38 (0.98 mmol/L)
- ECG: NSR, otherwise normal
- Blood profile normal (glucose, KFTs)
- AST 50 (1.1 ULN), ALT 80 (1.7 ULN), GGT normal
- Urinalysis: WNL

Medical history
- Sedentary lifestyle, many business lunches and evening meetings
- Sparse medical history - generally does not go to the doctor unless “he needs to”.
- 2012: ED visit for acute, colicky abdominal pain after returning from a business trip. RUQ U/S reported normal gall bladder, mild hepatomegaly, and diffuse fatty infiltration of the liver consistent with steatosis. Diagnosed with gastroenteritis and discharged home. No follow up.
- 2013: Seen by primary care for URI.

Questions
1. What is the technical definition of non-alcoholic fatty liver disease (NAFLD)? **Hepatic steatosis by imaging or biopsy, exclusion of significant alcohol consumption (<20 gms/d females, <30 gms/d males), exclusion of other causes of steatosis. On biopsy require > 5% steatotic hepatocytes.**
2. What general features differentiate non-alcoholic fatty liver (NAFL) from non-alcoholic steatohepatitis (NASH)? **Both have steatosis, but NASH is associated with hepatic inflammation that is histologically indistinguishable from alcoholic steatohepatitis and may include lobular inflammation, hepatocellular ballooning, and fibrosis.**
3. What are the main risk factors for development of NAFLD? **Obesity with >60% prevalence in those with BMI > 30, 90% if BMI > 39, diabetes, hypertriglyceridemia, and metabolic syndrome.**
4. What are the common lab findings in NAFL? **AST and ALT 2-5x ULN, AST/ALT ratio < 1, enzyme elevations do not predict degree of inflammation or fibrosis, enzymes can be normal.**
5. While NAFLD is associated with many conventional CV risk factors, is there any evidence that the presence of NAFLD may actually serve as an independent predictor of
CV outcomes? Yes, large meta-analysis found OR of 1.50 for CV events when other risks controlled.

6. What is the main mortality risk in this case? Studies are variable, but possible increased MRs in range of 1.34 – 1.69, mostly due to cardiovascular disease.

7. Is there any extra concern regarding the hepatomegaly? Hepatomegaly present in approximately 5-20% of those with NAFL – may indicate more advanced fibrosis.

8. How would you assess this applicant’s extra mortality risk? None to minimal.

Alternate Scenario

- BMI 36
- BP 152/90
- Father died of massive MI at age 52
- ECG with minor inferior T wave changes
- Insurance A1c 6.7
- AST 90 (2.1x ULN), ALT 123 (2.7x ULN)
- Mid-life crisis and is now seeking regular medical care.
- Seen by GI, live biopsy performed, Jan 2015. Findings include histologic grade 2 (mod) and fibrosis stage 2. He is counselled to adopt healthy lifestyle, see his primary care doctor to manage CV risks and take Vitamin E 400 IU/day. (Grade 2 = Steatosis of any degree; ballooning of hepatocytes (predominantly zone 3) obvious; intra-acinar polymorphonuclear cells noted, may be associated with zone 3 pericellular fibrosis; portal and intra-acinar chronic inflammation noted, mild to moderate. Stage 2 = Zone 3 perisinusoidal/pericellular fibrosis with focal or extensive periportal fibrosis.)

Questions

9. What impact does the presence of any inflammation on the biopsy have on the probability of progression to advanced fibrosis? 2.5x increased risk of progression.

10. What are other risk factors for disease progression? Older age, DM, AST and ALT > 2x ULN, ballooning degeneration, Mallory hyaline or fibrosis on biopsy, BMI > 28.

11. Have therapeutic interventions demonstrated any impact on disease progression (histologically proven)? Yes: Weight loss, bariatric surgery, vitamin E (NASH), TZDs, obeticholic acid. No: metformin, omega-3s, ursodeoxycholic acid.

12. How would you assess this applicant’s extra mortality risk? Moderate.
CASE #3

Application
- 23 year old female, non-smoker
- Recent college graduate, starting new job as communications director for non-profit organization
- Applying for 150,000 USD term life (convertible to whole of life without underwriting in first 10 years)

Insurance para-medical
- Self-reported: 5’3” (160 cm), 132 lbs. (60 kgs), BMI 23.4.
- Diagnosed with ulcerative colitis at age 19.
- Treated with mesalamine rectal suppositories, but no treatment for almost a year. Doing well, no symptoms.
- Family history: father and mother both alive and well. Older brother with ulcerative colitis since age 15, controlled on medication. Younger sister without medical history.
- Oral fluids negative for HIV, cotinine, and cocaine.

Questions
1. Do you have enough information in which to assess mortality risk? Possibly. One could very reasonably surmise that she likely has ulcerative proctitis and is now in remission.
2. Do you think a questionnaire or discretionary APS would be necessary or useful? Depends. A questionnaire would not likely give you much more information than you already have and an APS would likely only validate your reasonable assumptions.
3. What is the main mortality risk in this case? There is essentially no mortality risk in this case.

Alternate Scenario
- 32 year old male with history of ulcerative colitis (pancolitis) diagnosed at age 20 while in college.
- APS indicates on treatment with 5-ASA and infliximab. Last flare approximately 3 years ago. Colonoscopy 2 years ago with random biopsies every 10 cm from the cecum to the rectum revealed no evidence of dysplasia.

Questions
4. What two major risk factors determine the likelihood of developing colorectal cancer (CRC) in individuals with ulcerative colitis? Duration and extent of disease. Greatest over 10 years and in those with pancolitis.
5. How often does this individual require surveillance colonoscopy? Depending on the society, every 1-3 years.
6. What is his risk of developing colorectal cancer over time? The approximate cumulative incidence of CRC is 5 to 10 percent after 20 years and 12 to 20 percent after 30 years of disease and up to 30 percent after 35 years of disease.
7. What is his current overall mortality risk? **Moderate, although he is followed well and might be considered mild.**

**Alternate Scenario**
- Applicant’s colonoscopy 2 years ago demonstrated low grade dysplasia in one of the biopsies.
- He was to return for follow up colonoscopy in 6 months, but did not do so.

**Questions**
7. What is the risk that he might have CRC at the time of underwriting? **The management of low grade dysplasia is controversial. However, studies demonstrate that 19% have CRC at immediate colectomy and 34% have CRC at colectomy at 12 months.**
8. How would you assess his mortality risk? **Extremely high.**

**Alternate Scenario**
- Applicant’s most recent colonoscopy 1 year ago was normal. Due for next colonoscopy in another year.
- Current insurance labs: KFTs normal, ALT 45 U/L normal, AST 38 U/L normal, GGT 110 (1.7x ULN), alkaline phosphatase 140 U/L (1.2x ULN).

**Questions**
9. Are you concerned at all with regard to the low grade liver enzyme elevations? Why or why not? **It has been estimated that primary sclerosing cholangitis (PSC) occurs in approximately 5 percent of individuals with ulcerative colitis. It is more common in men with ulcerative colitis and in those with pancolitis.**
10. How would you assess his mortality risk? **Very high.**

**Alternate Scenario**
- Rather than ulcerative colitis, the applicant has Crohn disease.
- Screening colonoscopy 1 year ago was normal.
- Insurance labs are normal.

**Questions**
11. Is the CRC risk for Crohn disease the same as it is for ulcerative colitis? **It is probably comparable to the risk for ulcerative colitis although data is less conclusive. RR for CRC in Crohn disease is higher for those with disease confined to the colon and in those diagnosed with Crohn disease prior to age 30.**
12. Are there different surveillance recommendations for Crohn disease compared with ulcerative colitis? **In general, most societies recommend the same surveillance protocols for individuals with Crohn disease as ulcerative colitis, despite the fact that evidence may be lacking.**
13. What is the risk of developing PSC with Crohn disease compared with ulcerative colitis? **It may be slightly lower, approximately 3.5%.**
CASE #4

Application
- 57 year old male, smoker
- Works as an accountant
- Applicant admits to occasional alcohol use
- Applying for $1 million (US$) survivor policy

Insurance exam
- 5’10”, 232 lbs. (178 cm, 105.5 kg)
- BP 128/84, 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 and a sister in good health.
- Total cholesterol 198 (5.12 mmol/L), HDL 50 (1.29 mmol/L)
- Blood profile normal
- Urinalysis: within normal limits; positive for cotinine/nicotine

Medical history
- Applicant has a long history of esophageal reflux symptoms without dysphagia.
- An upper endoscopy in 2008 showed salmon colored mucosa in the distal esophagus compatible with Barrett’s esophagus that extended 5-6 cm from the gastro-esophageal (GE) junction.
- Biopsies at that time showed intestinal metaplasia with goblet cells and no dysplasia.
- Subsequent endoscopies in 2011 and 2014 showed similar findings on examination and pathology with no dysplasia
- Applicant has been treated with the proton pump inhibitor drug omeprazole which has largely controlled his symptoms.

Questions
1. What are the main risk factors for development of Barrett’s here? **Age, sex, history of GERD, obesity, smoking**
2. What is the main mortality risk in this case? **Adenocarcinoma of the esophagus**
3. Does this risk vary with age? **Yes, the rates increase with age. The estimated rates for development of adenocarcinoma are 0.02% per year for ages 30-49, 0.1% for ages 50-69 and 0.18% for age 70 up.**
4. Does the use of the proton pump inhibitor drug lower the risk? **It may help symptoms and/or improve esophagitis but does not reverse the metaplasia or reduce the risk of adenocarcinoma.**
5. Is the follow-up regimen adequate here? **It is controversial but most GI physicians would recommend follow-up endoscopy every 3-5 years in the absence of dysplasia.**
6. How would you assess the mortality risk? **Likely minimal to none with the absence of dysplasia and good follow-up regimen.**
Alternate Scenario

- Applicant’s endoscopy showed a short segment (< 3 cm of Barrett’s)

Questions

1. Does the length of the Barrett’s mucosa change the prognosis here? **Yes, the risk for dysplasia or cancer is lower with short segment Barrett’s**

Alternate Scenario

- Applicant’s initial biopsy showed reactive changes and possible low grade dysplasia
- Two subsequent biopsies show no dysplasia

Questions

1. Does the presence of low grade dysplasia change the risk? **Yes, probability of conversion to adenocarcinoma is increased to 0.6% per year.**
2. Is it likely that low grade dysplasia was present in this case? **No, it is often difficult for pathologists to differentiate low grade dysplasia from reactive changes. The subsequent negative follow-up would suggest that the original diagnosis of dysplasia may not be accurate.**
3. How would you assess the mortality risk here? **Likely closer to that in individuals with no evidence of dysplasia.**

Alternate Scenario

- Applicant’s most recent biopsy in 2013 showed high grade dysplasia
- He was treated with endoscopic laser ablation of the distal esophagus
- Two subsequent endoscopies with biopsy showed no evidence of Barrett’s or dysplasia

Questions

4. How does the presence of high grade dysplasia change the risk? **The probability of conversion to adenocarcinoma is increased to 4-6% per year.**
5. Has the Barrett’s and dysplasia been cured in this case? **No, it is often difficult for document eradication of the abnormal tissue as no pathology specimens are obtained with ablative therapy. In addition, during the healing process, normal mucosa may overlay the abnormal histology and shield it from biopsy sampling.**
6. What are other forms of treatment for high grade dysplasia? **Distal esophagectomy and mucosal resection.**
7. How would you assess the mortality risk with this scenario? **Moderate to high. The short term follow-up is encouraging but does not confirm that the risk for cancer development has been eliminated.**