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Hepatitis C Infection with Normal Liver Chemistry Tests

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Clinical Scenario

A 50 y/o man was recently diagnosed with chronic hepatitis C after a life insurance physical. He was very surprised by the diagnosis since he led an active lifestyle, exercised regularly, and did not smoke nor drink any alcohol, except a glass of wine once or twice per month. He had experimented with injecting drugs during his freshman year at college. Over the last 5 years, he had undergone regular physicals and never was told of any “liver problems”. In reviewing laboratory data from his referring provider, liver enzymes had been checked on two previous annual physicals with serum ALT activities of 44 and 41 U/L. Physical examination shows a healthy male, BMI =24, without any stigmata of chronic liver disease. Currently, serum ALT activity is 44 U/L and HCV RNA is >700,000 IU/mL with genotype 1. Platelet count was 244,000 cells/mm³.

The Dilemma

This patient is a generally healthy man who was likely infected with chronic hepatitis C for over 30 years prior to the consultation. Despite the prolonged duration of infection, he had no signs or symptoms of hepatitis C or advanced liver disease. There is historical evidence that his serum ALT activities have been persistently within the normal range. When confronted with such an individual, clinicians may speculate that aggressive treatment of hepatitis C in this vigorous patient is unwarranted. However, further evaluation and management can be planned only after considering the natural history of chronic hepatitis C infection with persistently normal ALT levels and the outcome of therapy in these patients.

Defining normal serum ALT activity

Elevations of serum alanine aminotransferase (ALT) and aspartate aminotransferases (AST) activity serve as important markers for liver injury. The finding of an abnormal ALT in a patient, even in the absence of clinical signs or symptoms, should prompt further evaluation for occult liver disease. Hereditary hemochromatosis, chronic viral hepatitis, and non-alcoholic steatohepatitis are frequently overlooked causes of asymptomatic ALT abnormalities that could have serious consequences over time. In order to define “abnormal ALT” which would prompt clinical investigation, healthcare providers must be confident in the definition of “normal” ALT, a value below which they can be secure that liver disease is unlikely. However, despite the importance of these definitions to general medical care and the seemingly simple dichotomy that should be represented by a laboratory test above or

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below a specific threshold, significant controversy exists as to the absolute value for a normal ALT.

Reference ranges for serum ALT activity vary widely across laboratories. An informal search of web resources indicate that the upper limit of normal ALT is generally between 40 and 50 U/L for males and slightly lower for females, although a 'normal' ALT value as high as 72 U/L was noted. How can the variability be explained and what are the clinical consequences of applying different thresholds for normality?

Reference ranges for serum ALT activity are often developed from the variance in results derived from a local "healthy" population. Thus, including subjects with occult liver disease in this reference group could spuriously raise the threshold for what is considered "normal" ALT activity. This possibility was examined in an important study from Italy. Prati and colleagues evaluated over 6000 first-time blood donors and examined the associations between clinical and laboratory factors and serum ALT levels¹. Serum ALT activity was associated with several risk factors for fatty liver disease including body mass index, blood glucose levels, and hypertriglyceridemia, among others. When only subjects with the lowest risk for liver disease were analyzed, the study suggested that the updated upper limit of normal ALT should be 30 U/L for males and 19 U/L for females.

The new reference range recommended by this study improved the sensitivity for identifying patients with liver disease but decreased the specificity. Adoption of these thresholds as normal could lead to a dramatic increase in the diagnosis of patients with occult liver disease, most due to non-alcoholic fatty liver disease, the impact of which is beyond the scope of this article. Nevertheless, the new reference range as suggested in this study does have clinical correlates in patients with chronic hepatitis C. As discussed below, patients with persistently "normal" ALT defined by local laboratories often have significant liver disease. Furthermore, when sustained virological response is achieved in these patients, the level of ALT activity often decreases to levels below 30 U/L, suggesting that necroinflammatory activity was indeed present before treatment.

Natural history of chronic hepatitis C with persistently normal ALT

Approximately 25% of patients with chronic hepatitis C have persistently normal ALT activity (PNALT), defined as serum ALT repeatedly within the "normal range" for a specified prolonged period of observation². Guidelines from the American Association for the Study of Liver Disease suggest that at least two ALT measurements within the normal range taken over at least 6 months can define those with PNALT³. However, it has long been recognized that serum ALT levels fluctuate in patients with chronic hepatitis C and flares of disease activity may occur at irregular intervals.

The absence of a gold standard for PNALT makes comparisons across studies difficult. Nevertheless, it is generally accepted that individuals with PNALT have more mild hepatic histology when compared to patients with persistently abnormal ALT. In a retrospective study, the necroinflammatory activity was negligible and the stage of fibrosis in 480 patients with PNALT was significantly lower compared to a large cohort of patients with abnormal ALT⁴ (Table). It should be noted that 10% of the PNALT cohort had stage 3 bridging fibrosis on liver biopsy⁴. Other cross sectional studies have shown that cirrhosis was present in 0–11% of patients with PNALT.

Several studies have attempted to evaluate the long-term outcome in patients with PNALT and all suggest that they have a slower rate of fibrosis progression (fibrosis score over estimated duration of infection) compared to patients with abnormal ALT activity. In a study of 24 patients with PNALT who underwent serial liver biopsies over a ten-year follow-up

period, fibrosis stage remained stable⁵. In aggregate, these data support the favorable natural history of HCV with PNALT, but the potential still exists for progression to advanced liver disease.

Response to antiviral therapy

Initial concerns that PNALT patients should be treated differently developed from early trials of standard interferon that demonstrated PNALT patients could have a flare of ALT during therapy or after treatment cessation, particularly in non-responders to treatment. The low overall chance of response with interferon monotherapy coupled with the potential for increasing disease activity discouraged the use of this agent in those with PNALT. Indeed, early registration trials for interferon and ribavirin combination therapy and peginterferon therapies all excluded patients with normal ALT at the time of screening, which hampered our understanding of the treatment response in this patient population. Subsequently, small studies of interferon in combination with ribavirin showed more favorable results with SVR rates as high as 50% in patients with normal serum ALT activity, similar to those reported in patients with abnormal ALT.

The largest randomized trial of patients with PNALT treated with peginterferon and ribavirin was reported by Zeuzem and colleagues⁶. Over 400 patients with PNALT (three measurements of ALT within the normal range during the 18 months prior to enrollment) were randomized (3:3:1) to receive peginterferon alfa-2a 180 µg/week and ribavirin 800mg/day for 24 or 48 weeks, or observation only. No patient in the observation arm achieved spontaneous viral clearance. The overall SVR was 30% for patients treated for only 24 weeks and 52% for patients treated for 48 weeks. As with all interferon-based studies, genotype had a major impact on treatment response. Genotype 1 patients had SVR rates of 13% and 40% in the 24 and 48 week arms, respectively, while genotype 2 and 3 had response rates of 72% and 78%. These results are consistent with studies that included only subjects with abnormal ALT levels, although in the present study the lower dose of ribavirin than is currently recommended for genotype 1 patients (1000–1200mg/day) likely compromised these results to some extent.

The evolution of serum ALT levels in this study of patients with purportedly PNALT is particularly instructive and further undermines the current accepted thresholds for normal ALT. The median baseline ALT value in this cohort was approximately 25 IU/L, well within the normal range. In those achieving sustained virological response, serum ALT activity further decreased and remained between 10 and 15 IU/L. In addition, 52% of patients with well-documented PNALT in the untreated arm had transient elevations of ALT above the upper limit of normal during the observation period.

Current treatment recommendations for hepatitis C with PNALT

Numerous evidence-based guidelines have been published by various governmental agencies and professional societies regarding management of patients with chronic hepatitis C and all of them have included comments about patients with persistently normal serum ALT activities. They generally recognize the difficulty in defining normal ALT for an individual patient, that the natural history in this subset of patients with chronic hepatitis C may be more benign, and that antiviral response is generally similar regardless of ALT levels. The most recent NIH Consensus Statement in 2002 acknowledged that “all patients with chronic hepatitis C are potential candidates for antiviral therapy”⁷. Qualifying statements for patients with normal ALT included that expert opinions differed on the need for biopsy and treatment for these patients and suggested that “numerous factors must be considered in recommending treatment, including favorable genotype, presence of hepatic fibrosis, patient motivation, symptoms, severity of comorbid illness, and the patient’s age”.

Excerpts from guidelines from the American Association for the Study of Liver Diseases³ recommend that “Regardless of the serum aminotransferases levels, the decision to initiate therapy with interferon and ribavirin should be individualized based on the severity of liver disease by liver biopsy, the potential of serious side effects, the likelihood of response, and the presence of comorbid conditions”.

Recently published guidelines by the American Gastroenterological Association suggest that “Patients with normal ALT activity are candidates for antiviral therapy or for monitoring without intervention as determined on an individual basis and as influenced by patient factors such as motivation, genotype, histologic activity, and fibrosis”^{8,9}.

Recommendations

Patients with chronic hepatitis C and persistently normal ALT should be evaluated in a similar manner to patients with chronically abnormal ALT levels, such as screening for other chronic liver diseases including hemochromatosis. During the initial consultation, I would provide reassurance about the natural history of chronic hepatitis C in those with PNALT. However, I would also stress the uncertainties of this information and our limited ability to predict outcome over the ensuing decades. I would evaluate this patient’s candidacy for antiviral therapy and probe if there were any contraindications to peginterferon and ribavirin treatment. During a discussion about the probabilities of sustained virological response versus the potential side effects associated with combination antiviral therapy, I would assess the patient’s level of enthusiasm for undergoing treatment. For African American patients, the likelihood of sustained virological response is significantly lower than Caucasian patients and this must be factored into the discussion as well¹⁰.

I would also suggest a liver biopsy in this patient to assess grade and stage in order to provide prognostic information that may be helpful as he contemplates antiviral therapy. For patients with genotype 2 or 3, liver biopsy is more likely to be deferred in light of the higher likelihood of sustained virological response, although alcohol use and the potential for hepatic steatosis or advanced fibrosis, among other factors, may lead to biopsy in individual cases. Liver biopsy before therapy is not mandatory, particularly for individuals who are certain that they would like to begin treatment. The results of liver biopsy must be interpreted cautiously due to the well-documented potential for sampling error. Non-invasive serum panels of hepatic fibrosis may provide supplementary evidence regarding stage of liver disease but also suffer from significant limitations¹¹. Thus, providers must use all available clinical information as they counsel the patient about disease severity and potential for progression.

During a follow-up visit after the patient has had the opportunity to reflect on our initial discussion, we would review biopsy results and again discuss therapeutic options. For patients with moderate to severe hepatic histology (>stage 2), antiviral therapy should be encouraged. For milder liver disease (stage 0–1), patients may choose to defer treatment although follow-up biopsy in 3–5 years should be considered to verify stable disease. My general recommendation is that good treatment candidates (without contraindications) undergo antiviral therapy with peginterferon and ribavirin, regardless of hepatic histology, if they are sufficiently motivated. The probability of sustained virological response usually outweighs the manageable risks associated with treatment.

Suggested Reading

1. Prati D, Taioli E, Zanella A, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann Intern Med.* 2002; 137:1–10. [PubMed: 12093239]

2. Zeuzem S, Alberti A, Rosenberg W, et al. Review article: management of patients with chronic hepatitis C virus infection and “normal” alanine aminotransferase activity. *Aliment Pharmacol Ther.* 2006; 24:1133–49. [PubMed: 17014573]
3. Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. *Hepatology.* 2004; 39:1147–71. [PubMed: 15057920]
4. Shiffman ML, Diago M, Tran A, et al. Chronic hepatitis C in patients with persistently normal alanine transaminase levels. *Clin Gastroenterol Hepatol.* 2006; 4:645–52. [PubMed: 16630770]
5. Persico M, Perrotta S, Persico E, et al. Hepatitis C virus carriers with persistently normal ALT levels: biological peculiarities and update of the natural history of liver disease at 10 years. *J Viral Hepat.* 2006; 13:290–6. [PubMed: 16637858]
6. Zeuzem S, Diago M, Gane E, et al. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. *Gastroenterology.* 2004; 127:1724–32. [PubMed: 15578510]
7. National Institutes of Health. Gastroenterology; Consensus Development Conference Statement: Management of hepatitis C 2002; June 10–12, 2002; 2002. p. 2082-99.
8. Dienstag JL, McHutchison JG. American Gastroenterological Association medical position statement on the management of hepatitis C. *Gastroenterology.* 2006; 130:225–30. [PubMed: 16401485]
9. Dienstag JL, McHutchison JG. American Gastroenterological Association technical review on the management of hepatitis C. *Gastroenterology.* 2006; 130:231–64. quiz 14–7. [PubMed: 16401486]
10. Conjeevaram HS, Fried MW, Jeffers LJ, et al. Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. *Gastroenterology.* 2006; 131:470–7. [PubMed: 16890601]
11. Parkes J, Guha IN, Roderick P, Rosenberg W. Performance of serum marker panels for liver fibrosis in chronic hepatitis C. *J Hepatol.* 2006; 44:462–74. [PubMed: 16427156]

Figure 1.
Algorithm for management of patients with hepatitis C and persistently normal ALT.

Table 1

Clinical characteristics of patients with hepatitis C and persistently normal serum ALT activity compared to patients with abnormal ALT (adapted from reference 4)

	PNALT (n=480)	Abnormal ALT (n=1993)
Female gender	59%	32%
Mean weight	74 kg	77 kg
Mean HCV RNA ($\times 10^6$ copies/ml)	3.1	6.0
Knodel Necroinflammatory Grade		
<5	65%	11%
5–10	34%	78%
>10	1%	11%
Knodel Fibrosis Stage		
Mean fibrosis score	0.9	1.4
Stage 0	27%	5%
Stage 1	64%	71%
Stage 3	10%	24%
Stage 4	0%	0%