Author's response to reviews

Title: Recurrence of hepatitis C virus during leucocytopenia and spontaneous clearance after recovery from cytopenia

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Author's response to reviews: see over
Dear Professor Kidd,

thank for reviewing our case report. The comments of the three reviewer are very helpful and are answered in our point by point reply and included in the revised version our case report entitled: “Recurrence of hepatitis C virus during leucocytopenia and spontaneous clearance after recovery from cytopenia”.

Point by point reply to the reviewers comments:

Reviewer 1, Curtis L. Cooper:

1. Dr. Cooper raised the question whether the patient was infected acutely or chronically:

Retrospective our diagnosis of acute hepatitis C was supported by several data: Patient’s wife was diagnosed with acute hepatitis C two weeks after his diagnosis. During follow-up both had a documented spontaneous viral elimination. Spontaneous clearance of chronic hepatitis C is a rarity. As a possible risk factor both had made an ozone therapy at an alternative practitioner several weeks before onset of acute disease. Other reason for elevated liver enzymes (infections, metabolic
or toxic reasons) were excluded. Taken these facts together in our opinion diagnosis of acute hepatitis C is beyond question. These facts are now included in our case report.

2. He also pointed out that HCV-RNA levels fluctuates in the initial six months, although the usual HCV RNA variability is 0.5-1.0 log 10:

We agree that fluctuations of HCV RNA had been described during acute HCV infection. However these fluctuations have been described during the initial 4-8 weeks as within the manuscript (J Virol. 2005 May; 79(10): 6023-34.) cited by the 2. Reviewer Dr. Mangoni (see also reviewer 2, point 1). To our knowledge no fluctuation 5 log 10 six months after acute infection has been described so far. This is also in line with a paper in Gastroenterology 2003; 125: 80-88. In this very large cohort of patients with acute hepatitis C none of the patients displayed and HCV RNA variability of 5 log10 at all.

Reviewer 2, Emanuele Durante Mangoni:

1. Dr. Morgani classifies our finding of HCV RNA fluctuation as common clinical finding. As for reviewer 1 (point 2) this does not hold true on closer inspection. The fluctuations described in the cited paper by Lavillette et al. (J Virol. 2005 May; 79(10): 6023-34.) are all during the very early phase of infection. No fluctuations of HCV-RNA were described in this manuscript later than 12 weeks after infection! Week 0 was the time of infection in their cohort but not the onset of disease as for our patient. Taking the rise of ALT as onset of acute disease as week 0 and onset of acute disease (onset of symptoms corresponds to our baseline week 0) fluctuations of HCV RNA were not detected later than 4 weeks after onset of acute disease. The reason for this is that in the manuscript by Lavillette et al. a unique cohort of hemodialysis patients during a nosocomial outbreak could be followed from time of infection weeks before onset of symptoms.

2. Dr. Morgani states that granulocytes have no role in controlling HCV replication. HCV is rather under control of CD4+ and CD8+ T lymphocytes.
We agree to this statement. Our own former data and publications concerning HCV specific CD4+ and CD8+ T cell response have contributed to this understanding. We think that the term agranulocytosis was misleading and therefore now introduced the term leucocytopenia. In our patient not only the granulocytes but also lymphocytes were diminished significantly. We also believe that the drop of lymphocytes plays the key role for reappearance of HCV-RNA.

Reviewer 3, Tilman J Gerlach.

1. Details of propythiouracil treatment are now included in the manuscript.

2. Most likely mode of infection is now included in the manuscript. Patient and his wife had underwent an ozone therapy at an alternative practitioner and both developed acute selflimiting hepatitis C. This mode of infection by ozone therapy has been described several times before.

3. Dr. Gerlach requested HCV RNA values at least six months after the last positive HCV RNA. Fortunately we have seen the patient in the meantime since the first submission of our manuscript. 47 weeks after onset of acute disease he is still HCV RNA negative, indicating sustained spontaneous viral clearance. We have introduced these data in our table and result section.

We hope that we have answered satisfactorily to the reviewers concerns and hope that our case report is now suitable for publication in your Journal of Medical Case Reports.

Thank you very much in advance.

Prof. Dr. M.C. Jung

Dr. N. Grüner