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12/10/2024

Prof. Salem Youssef Mohamed

**Rebuttal letter and revised manuscript:**

Dear Editor,

This document contains responses to the comments of reviewers which were very helpful. We have made changes to improve the paper in response to this review. The revised manuscript is attached with changes highlighted in red. The list of changes against each comment of reviewers is summarized in the tables below. We thank you and the reviewers for your efforts in evaluating and improving this manuscript.

Kind regards,

SOUALAH Thouraya, on behalf of the other authors

**Reply to comments of Reviewer 1:**

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| Comments of reviewer | Reply to comments |
| Can you send the approval for publication from the patients who participated in your study? | please find the attached signed consent |
| Could you explain myelodysplastic syndrome due to HCV infection or due to his history of smoking and drug addiction? | Haematological abnormalities in liver cirrhosis are multifactorial which include, portal hypertension-induced sequestration, diminished bone marrow stimulating factors and direct viral or toxin effect on bone marrow**[14]**. Our case presented a pancytopenia with a compensated liver cirrhosis due to HCV infection at an early stage of portal hypertension (portal vein dilated at 17mm with mild splenomegaly) without evidence of portosystemic shunt but preserved liver functions, a history of abstinence from alcoholism and drug abuse since 2016 but concomitantly diagnosed with acute elevated hepatic enzymes and very high HCV viral load. On the other hand, the achievement of complete resolution of the haematological abnormalities after initiation of the antiviral therapy even though, the patient never stopped smoking, makes it clear and cut that, these abnormalities are strongly related to the HCV activity. |
| Can you tell us if the patient received any chemotherapy or steroids during AAD? | The patient was started exclusively on Sofosbuvir/Daclatasvir in September 2022 for 24 weeks and blood transfusions at an average rate of 2/month for 15 months. |
| You did not mention any presentation about MDS for this patient. | the main presentation of MDS as mention in the case presentation section was pancytopenia confirmed by bone marrow analysis.  In the discussion section:  Our case presented dysplastic changes affecting > 10% cells of all lines, absent blasts, slight reticulin densification and no evidence of malignant cellular infiltration. The patient had no genetic mutation nor a history of familial similar cases, absent current history of exposure to alcoholism, drugs or occupational risk factors. The patient was diagnosed as morphologically defined myelodysplastic syndrome (MDS) with low blasts according to the 2023 WHO classification criteria, at an intermediate estimated Revised International Prognostic Scoring System risk (IPSS-R) and an intermediate comorbidity risk**[8-9]**. |

**Reply to comments of Reviewer 2:**

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| --- | --- |
| Please check the author names | **Thouraya Soualah,****Mustapha Lahcene, Lynda Chikhi, Fatima Zohra Sadar**. |
| Please include up to 10 keywords in your revised manuscrip | **Key words:** Chronichepatitis C; Myelodysplastic neoplasm; Liver cirrhosis; Pancytopenia; Haematological manifestations; Lymphoprolefirative disorders; Myelogenous disorders; Direct acting antiviral drugs. |
| Please amend the references as per the author's guidelines | **References**   1. Songtanin B and Nugent K. Burden, Outcome, and Comorbidities of Extrahepatic Manifestations in Hepatitis C Virus Infection. Biology 2023;12:1-23. 2. Cacoub P, Comarmond C, Vieira M, Régnier P and Saadoun D. HCV-related lymphoproliferative disorders in the direct-acting antiviral era: From mixed cryoglobulinaemia to B-cell lymphoma. J Hepatology 2022;76: 174–185. 3. Salama II, Raslan MH, Abdel-Latif AG et al. Impact of direct-acting antiviral regimens on hepatic and extrahepatic manifestations of hepatitis C virus infection. World J Hepatol 2022;14:1053-1073. 4. Mazzaro C, Quartuccio L, Adinolf LE et al . A Review on Extrahepatic Manifestations of Chronic Hepatitis C Virus Infection and the Impact of Direct-Acting Antiviral Therapy. Viruses 2021;13:2249. 5. ‌Park H, Chen C, Wang W, [Henry](https://pubmed.ncbi.nlm.nih.gov/?term=Henry+L&cauthor_id=28873225) L , [Cook](https://pubmed.ncbi.nlm.nih.gov/?term=Cook+RL&cauthor_id=28873225) RL and [Nelson](https://pubmed.ncbi.nlm.nih.gov/?term=Nelson+DR&cauthor_id=28873225) DR. Chronic hepatitis C virus (HCV) Increases the Risk of Chronic Kidney Disease (CKD) While Effective HCV Treatment Decreases the Incidence of CKD. Hepatology 2018;67:492–504. 6. Pozzato G, Mazzaro C, Maso LD et al. Hepatitis C virus and non-Hodgkin’s lymphomas: Meta-analysis of epidemiology data and therapy options. World J Hepatol 2016;8:107-116. 7. Cacoub P and Rosenthal E. Extrahepatic manifestations in chronic hepatitis C virus carriers. Lupus 2015; 24:469–482. 8. Nachtkamp K, Kobbe G, Gattermann N and [Germing](https://pubmed.ncbi.nlm.nih.gov/?term=Germing+U&cauthor_id=36718105) U. Myelodysplastic syndromes: new methods of diagnosis, prognostication, and treatment. Dtsch Arztebl Int 2023;120:203-10. 9. Fenaux P, Haase D, Santini V, [Sanz](https://pubmed.ncbi.nlm.nih.gov/?term=Sanz+GF&cauthor_id=33221366) GF, [Platzbecker](https://pubmed.ncbi.nlm.nih.gov/?term=Platzbecker+U&cauthor_id=33221366) U and [Mey](https://pubmed.ncbi.nlm.nih.gov/?term=Mey+U&cauthor_id=33221366) U . Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncology 2021;32:142-156 10. Asfour IA, Ayoub MS, Magid NAA and Elsaharty AAI. Evaluation of bone marrow examination in patients with hepatitis C virus infection. Egypt J Haematol 2013;38:13-16. 11. El Husseiny MN, Mohamed AS and Matta MM. Myelodysplastic Syndrome: An Egyptian Experience. J Blood Disord Transfus 2012;3:1-4. 12. Ciufu C, Arama V, Bumbea H, [Dobrea](https://pubmed.ncbi.nlm.nih.gov/?term=Dobrea%20C%5BAuthor%5D) C, [Ion](https://pubmed.ncbi.nlm.nih.gov/?term=Ion%20I%5BAuthor%5D) I and [Vladareanu](https://pubmed.ncbi.nlm.nih.gov/?term=Vladareanu%20A%5BAuthor%5D) AM. Correlations of hematological parameters with bone marrow findings in chronic lymphoproliferative disorders associated with hepatitis viruses. J Medicine Life 2013;6:464-471 13. Anderson LA, Pfeiffer R, Warren JL et al. Hematopoietic malignancies associated with viral and alcoholic hepatitis. Cancer Epidemiol Biomarkers Prev. 2008;17:3069–307 14. Qamar AA and Grace ND. Abnormal hematological indices in cirrhosis. [Can J Gastroenterol.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2721814/) 2009 Jun; 23(6): 441–445. 15. Klco JM, Geng B, Brunt ME et al. Bone marrow biopsy in patients with hepatitis C virus infection: Spectrum of findings and diagnostic utility. Am J Hematol. 2010;85:106–110. 16. Boada M and Grille S. Myelodysplastic syndrome in patients living with HIV infection. HEMATOL TRANSFUS CELL THER. 2023;45:119−123 17. Pawlotsky JM, Negro F, Aghemo A et al. EASL recommendations on treatment of hepatitis C:Final update of the series.J Hepatol 2020;73:1170-1218. |
| References should appear as a number, i.e., [1, 2] in the text. | A Romanian study assessing the bone marrow findings of 42 patients presenting a concomitant chronic lymphoproliferative disorder (CLD) and viral hepatitis (HCV=22, HBV=17, coinfection HCV+HBV ± HDV =3). 6 patients presented myelodysplasia with a concomitant indolent nonaggressive form of CLD out of which, 5 where HCV positive as to only one reported case of HBV **[12]**. |
| Please add the scale bar, annotations, magnifications, and program that generated these figures. Also, it is better to submit figures with high resolution and brightness. | **Bone marrow aspirates analysed by Leisca microscope DM 750 using May-Grünwald Giemsa stain** |

**Other changes made:**

1. Abstract:

* Elaboration on the risk factors the patient was exposed to ( smoking, previous history of alcoholism and drug abuse)
* Lying enfaces that the patient was exclusively treated with DAA and blood transfusions.

1. Case presentation:

* Patient had a previous history of intra venous drug abuse, intermittent alcohol consumption at an average of twice /year and unprotected sex with abstinence for 6 years before the time of diagnosis.

1. Discussion:

* 6th paragraph: elaborating that smoking could be a risk factor for developing MDS in HCV infection as to age and duration of exposure to HCV.
* 7th paragraph : attributing the myelodysplastic changes to the HCV infection rather than smoking or alcoholism.

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