**Comments from the Board of Editors and Reviewers:**

Dear Dr. van de Meeberg,

Thank you for submitting your manuscript to our peer reviewed, online and open access journal; the details of your submission are listed below.

Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 28076

Title: Hepatosplenic T-cell lymphoma in a 47-year-old patient with Crohn's disease on thiopurine monotherapy.

Author Name: Maartje M. van de Meeberg

Received Date: 2016-06-26 05:52:17

We are pleased to inform you that one of the peer reviewers has completed their review of your manuscript.

Thank you for your cooperation!

If you have any questions, please feel free to contact us via e-mail at:

Best regards,

Lian-Sheng Ma, President and Company Editor-in-Chief

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**Reaction to comments**

**World Journal of Gastroenterology**

**Damian Garcia-Olmo, MD, PhD, Doctor, Professor, Surgeon,**

Department of Surgery, Universidad Autonoma de Madrid;

Department of General Surgery, Fundacion Jimenez Diaz University Hospital,

Madrid 28040, Spain

Den Bosch, 20-8-2016

Dear editors,

Please find enclosed a revised version of our manuscript "Hepatosplenic T-cell lymphoma in a 47-year-old patient with Crohn's disease and thiopurine monotherapy" (ESPS Manuscript NO: 28076). We would like to thank the editors of World Journal of Gastroenterology for their positive assessment of our manuscript. We appreciate the constructive comments and we have adapted our manuscript according to the suggestions made by the editor and reviewer. All comments have been addressed in the enclosed point-by-point response.

We sincerely hope that we have fulfilled your requirements and that this version of our manuscript meets your expectations. We are looking forward to your response.

On behalf of the co-authors,

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**Reviewer #1**

Classification: Grade B, Very good.

Language evaluation: Grade B, minor language polishing.

Conclusion: Minor revision

The paper is interesting, well-written and reports a rare case of hepatosplenic T-cell lymphoma in a patient aged 47 years with Crohn's disease. The literature is described also well, the authors report in detail information regarding the other patients affected from this rare condition. I had some minor suggestions:

**1. English language should be improved by a professional editing service, in some points there are logic and grammatical errors**

First of all we would thank reviewer 1 for his time and dedication to criticize our manuscript.

The English grammar has been critically appraised by a certified medical doctor (International Bacculaureate, grade A2) and changes are made to the manuscript, such as:

- "Higher incidence is reported" instead of "The incidence is increased" (Page 3, line 44)

- "specifically" instead of "especially" (Page 3, line 45)

- "for over 2 years" instead of "more than 2 years" (Page 3, line 47)

- "In addition" instead of "On top of that" (Page 3, line 68)

- "Although" instead of "but" (Page 5, line 97)

- "was treated with" instead of "used" (Page 6, line 116)

- ´ for one-and-a-half years" instead of "during 1.5 years" (Page 6, line 120)

- “anaemia” changed in “anemie” according to American grammar (Page 4, line 86. Page 7, line 130. Page17, table 3)

- “high dose corticosteroids were administered, and subsequently by chemotherapy” instead of “high dose corticosteroids were started followed by chemotherapy” (Page 7, line 139-140)

- “In contrast with” instead of “in contrast to” (Page 8, line 149)

- “initiation” instead of “start” (Page 10, line 179)

- “should“ instead of “has to” (Page 10, line 196)

- “at an age older than 35 years” instead of “above the age of 35 years”(Page 10, line 188. Page 11, line 208)

- “could have been considerd” instead of “could be considerd” (Page 11, line 204)

- “Years of thiopurine treatment” instead of “Years of use thiopurine” (Page 17, line 251, table 3)

Moreover, we made extensive style improvements, mainly concerning word order.

In addition:

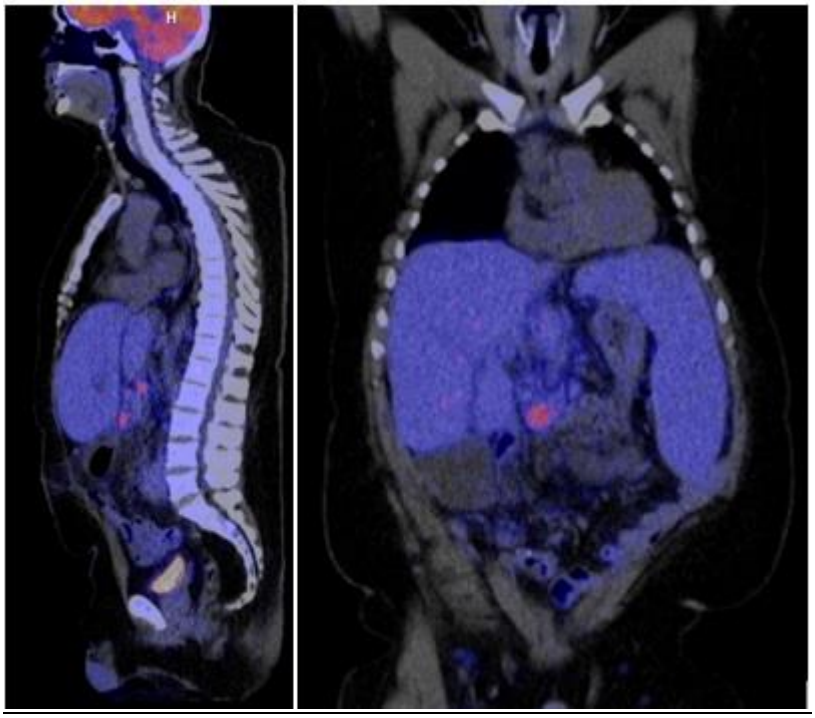
- We changed table 1a (page15) by using only the abbreviation s for the analysis in the table.

- We changed the title of the manuscript: “Hepatosplenic T-cell lymphoma in a 47-year-old Crohn’s disease patient on thiopurine monotherapy.” Instead of “Hepatosplenic T-cell lymphoma in a 47-year-old patient with Crohn’s disease on thiopurine monotherapy.”

**2. It could be interesting to report imaging findings (eg. ultrasound and endoscopy) in separate figures.**

Thank you for this comment. As suggested, we added the positron emission tomography of the patient showing hepatosplenomegaly with increased metabolic activity in liver, spleen and bone marrow (Figure 1). Indeed, this may better illustrate the location of HSCTL. We did not incorporate endoscopy figures since our case is mainly focused on HSTCL instead of CD.

Figure 1: Positron emission tomography showing hepatosplenomegaly with increased metabolic activity in liver, spleen and bone marrow. Left: coronal plane. Right: sagittal plane.



**3. Please discuss how and in what percentage immunosoppressive drugs (in particular thiopurine) can increase the risk of malignant disorders**

We would like to thank the reviewer for highlighting this point. We expanded a section in the discussion to discuss cancer risk in IBD patients on thiopurines. We added the following part to answer the first quest "how immunosuppressive drugs can increase the risk of malignant disorders": *Thiopurine cytotoxicity is mediated by the incorporation of 6-thioguanine during DNA replication in targeted cells, instead of guanine,*

*which ultimately leads to apoptosis. [10].* (Page 9, line 166-168). According the subject of this case report, we focused on thiopurines only.

In what percentage immunosuppressive drugs can increase immunosuppressive drugs is discussed in the introduction. See: *The estimated absolute risk to develop HSTCL in IBD patients treated with combination therapy is 1:22,000 in general and 1:3,534 for men younger than 35 years old. By contrast, IBD patients on thiopurine monotherapy had an estimated absolute risk of, respectively 1:45,000 and 1:7,404, in general IBD patients and in men younger than 35 years old[4-6].* (Page 5, Line 100-106)

We added the following part in the discussion to highlight the possible effects of thiopurines: *In IBD patients, thiopurine treatment is associated with a significantly increased overall risk (rate ratio = 1.41) of developing cancer[13], specifically non-melanoma skin cancer (NMSC), urinary tract cancers and lymphoproliferative disorders (multivariate adjusted hazard ratio of 5.28)[10, 14].*

*More specifically, thiopurines promote development of lymphomas: a recent meta-analysis found an overall standard incidence ratio for lymphoma of 5.7 in IBD patients receiving thiopurines, but not in patients formerly treated with thiopurines or patients who had never used these drugs[4]. The excess risk can be reversed by thiopurine withdrawal[10].* (Page 9, line 158 – 166)

**4. Please report more information on clinical findings, epidemiology, diagnosis, treatment and prognosis of hepatosplenic T-cell lymphoma**

Thank you for this suggestion. We aimed to write a compact case report focused on one case with IBD and HSTCL. However, as suggested by reviewer 1 we expanded the introduction with additional data regarding HSTCL epidemiology, clinical aspects and treatment modalities.

*As a consequence, patients present with hepatomegaly (77%), splenomegaly (96%), constitutional symptoms (70%), anemia (85%), thrombocytopenia (89%), leukopenia (72%) and liver enzyme abnormalities (46%), in the absence of lymphadenopathy[3]. HSTCL mainly affects male[4] adults with a median age of 20 to 35 years[1][3]. HSTCL has a rapidly*

*progressive course with a mean overall survival less than 16 months, regardless of the available treatment modalities (chemotherapy, splenectomy, bone marrow or stem cell transplantation)* [3] (Page 5, line 84-92)

**5. Is there any innate risk of hepatosplenic T-cell lymphoma in patients with Crohn's disease ? Please discuss more of this aspect also reporting evidence from the literature.**

Thank you for this suggestion. There is an innate higher risk for patients with Crohn disease to develop a lymphoma. There are conflicting results reported on this issue. As written in the ECCO Guideline (Annesse et al, Journal of Crohn's and Colitis, 2015, 1–21): "ECCO Statement 3A: IBD patients show a trend toward higher risks of developing haematological malignancies. Compared with the generalpopulation, UC patients are significantly more likely to develop leukaemia, whereas those with CD are at higher risk for lymphoma, especially non-Hodgkin lymphoma .

We wrote this in our discussion: *IBD patients, especially CD patients, are twice more likely to develop any lymphoma, regardless of immunosuppressive treatment*[9, 10]. (Page 9, line 153-154).

By our knowledge, it is unknown if patients with Crohn's disease have a higher risk to develop HSTCL regardless of immunosuppressive therapies.

We discuss the following in the second part of the introduction: *The estimated absolute risk to develop HSTCL in IBD patients treated with combination therapy is 1:22,000 in general and 1:3,534 for men younger than 35 years old. By contrast, IBD patients on thiopurine monotherapy had an estimated absolute risk of, respectively 1:45,000 and 1:7,404, in general IBD patients and in men younger than 35 years old*[4-6]. (Page 5, line 100-106)

**Reviewer #2**

Classification: Grade B, Very good.

Language evaluation: Grade A, priority publishing

Conclusion: Accept

The case report is well written and has the appropriate level of details to comprehend the course of disease for the case subject. The review of the literature pertaining to HSTCL in IBD is through. Criticisms:

**1. It is not clear what the duration of disease remission was either before or after the patient received a permanent ileostomy.**

First of all we would thank reviewer 2 for his time and dedication to criticize our manuscript.

We agree with the reviewer that duration of disease remission was unclear in the case report and added this as follows: *During his course of CD, he underwent both right and left hemicolectomy (at the age of 18 and 30 years, respectively) and received a permanent ileostomy at the age of 41 due to active perianal fistulating disease in the three years before. CD had been in remission in the five years preceding presentation at our hospital.* (Page 7, line 121-126)

**2. It would be good to briefly outline the number of reports of HSTCL in other autoimmune diseases like Rheumatoid arthritis.**

Thank you for this valuable comment. Indeed, RA patients were also at increased risk to develop HSTCL. We incorporated this in the manuscript as follows:

*IBD patients, especially CD patients, are twice more likely to develop any lymphoma, regardless of immunosuppressive treatment[9, 10]. The risk to develop HSTCL is also increased in auto-immune disorders like rheumatoid arthritis[11, 12], specifically in those patients, treated with TNF- a inhibitors, and in immunocompromised patients with, among others, renal or heart transplant[3].* (Page 9, line 153-157)

**3. The authors should also state the median time from initiation of thiopurines to HSTCL development among the 7 reported cases above the age of 35 years.**

Unfortunately the duration of using thiopurines is unknown in 4 of the 7 cases. We state the time of initiation of thiopurines to HSTCL in the other three cases. See:

*Only 7 CD cases are known to develop HSTCL at an age older than 35, all of them were receiving combination therapy (Table 2)[7, 15]. Time to HSTCL development following initiation of thiopurine treatment was reported in three cases, including 5.5, 7.3 and 13.5 years.* (Page 10, line 187 – 191).