

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 83901

**Title:** Case report on co-existing squamous cell carcinoma and chronic myelomonocytic leukemia with ASX Y and EZH2 gene mutations.

**Provenance and peer review:** Unsolicited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 05224683

**Position:** Peer Reviewer

**Academic degree:** DSc, MSc

**Professional title:** Postdoc, Postdoctoral Fellow, Research Scientist, Senior Scientist

**Reviewer's Country/Territory:** Bangladesh

**Author's Country/Territory:** China

**Manuscript submission date:** 2023-02-16

**Reviewer chosen by:** Geng-Long Liu

**Reviewer accepted review:** 2023-03-21 13:06

**Reviewer performed review:** 2023-03-21 15:28

**Review time:** 2 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



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<b>Scientific significance of the conclusion in this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

#### SPECIFIC COMMENTS TO AUTHORS

squamous cell carcinoma and chronic myelomonocytic leukemia with ASXL1 and EZH2 gene mutations is very important to identify the mechanism.

## PEER-REVIEW REPORT

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**Peer-review model:** Single blind

**Reviewer's code:** 05430684

**Position:** Peer Reviewer

**Academic degree:** MD, MSc, PhD

**Professional title:** Consultant Physician-Scientist

**Reviewer's Country/Territory:** Greece

**Author's Country/Territory:** China

**Manuscript submission date:** 2023-02-16

**Reviewer chosen by:** Geng-Long Liu

**Reviewer accepted review:** 2023-03-22 07:50

**Reviewer performed review:** 2023-03-25 08:27

**Review time:** 3 Days

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation

<b>Scientific significance of the conclusion in this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous
	Conflicts-of-Interest: <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS

I studied carefully the manuscript entitled "Case report on co-existing squamous cell carcinoma and chronic myelomonocytic leukemia with ASXL1 and EZH2 gene mutations" by Deng L-J et al. The manuscript describes a rare case of co-existence of chronic myelomonocytic leukemia (CMML) and non-small cell lung cancer (NSCLC). The diagnostic and therapeutic approach of the patient is challenging, thus rendering the manuscript of interest to the specialized readership. Despite its potential interest, the manuscript has to be further elaborated and clarified. Therefore, some comments added below might be useful to the authors. Major comments

1. The authors state in the "Abstract" section that "CMML cells did not infiltrate the lung cancer tissue". The presence of pulmonary leukemic infiltrates in CMML is extremely rare and is very well discussed in the paper of Fayed M et al. (see: Fayed M, Evans T, Abdulhaq H. Leukemic infiltration in the settings of acute respiratory failure. *Oxf Med Case Reports*. 2019 Dec 9;2019(11):482-485. doi: 10.1093/omcr/omz118. PMID: 31844533; PMCID: PMC6902626.). The authors are awaited to extend their discussion on the topic.
2. The authors state, in the "Abstract" section, that "the two malignancies occurring simultaneously did not

originate from the same cancerous cells". This is practically self-evident since CMML is a clonal disorder driven by progressively acquired somatic mutations in hematopoietic stem cells, while NSCLC implicates tissue-resident macrophages, which are independent of adult haematopoiesis, in the tumorigenesis process (see: Casanova-Acebes M, Dalla E, Leader AM, LeBerichel J, Nikolic J, Morales BM, Brown M, Chang C, Troncoso L, Chen ST, Sastre-Perona A, Park MD, Tabachnikova A, Dhainaut M, Hamon P, Maier B, Sawai CM, Agulló-Pascual E, Schober M, Brown BD, Reizis B, Marron T, Kenigsberg E, Moussion C, Benaroch P, Aguirre-Ghiso JA, Merad M. Tissue-resident macrophages provide a pro-tumorigenic niche to early NSCLC cells. *Nature*. 2021 Jul;595(7868):578-584. doi: 10.1038/s41586-021-03651-8. Epub 2021 Jun 16. PMID: 34135508; PMCID: PMC8923521.). The authors are wellcome to further clarify the certain phrase. 3. The authors state, in the "Discussion section" that "With a rate of 40%, ASXL1 gene mutation is thought to be related to CMML as an independent adverse prognostic factor affecting CMML survival. In contrast, with a rate of 5%, EZH2 gene mutations have no clear clinical impact on CMML.". In fact, Patniak et al. have demonstrated that the co-existence of ASXL1 and EZH2 gene mutations aggravate the clinical course of CMML patients; the median survival for ASXL1/EZH2 co-mutated CMML patients was 16 months, in comparison to 20 months for ASXL1mt/EZH2wt and 33 months for ASXL1wt/EZH2wt patients ( $p < 0.0001$ ) - see: Patnaik MM, Vallapureddy R, Lasho TL, Hoversten KP, Finke CM, Ketterling R, Hanson C, Gangat N, Tefferi A. EZH2 mutations in chronic myelomonocytic leukemia cluster with ASXL1 mutations and their co-occurrence is prognostically detrimental. *Blood Cancer J*. 2018 Jan 22;8(1):12. doi: 10.1038/s41408-017-0045-4. PMID: 29358618; PMCID: PMC5802714. Furthermore, Castaño-Díez S et al. reported that their three patients with the ASXL1/EZH2 co-mutation had an OS of 2.5 months vs. 35.2 months for those without the co-mutation ( $p = 0.001$ ) - see: Castaño-Díez S, López-Guerra M, Bosch-Castañeda C, Bataller A,

Charry P, Esteban D, Guijarro F, Jiménez-Vicente C, Castillo-Girón C, Cortes A, Martínez-Roca A, Triguero A, Álamo JR, Beà S, Costa D, Colomer D, Rozman M, Esteve J, Díaz-Beyá M. Real-World Data on Chronic Myelomonocytic Leukemia: Clinical and Molecular Characteristics, Treatment, Emerging Drugs, and Patient Outcomes. *Cancers* (Basel). 2022 Aug 25;14(17):4107. doi: 10.3390/cancers14174107. PMID: 36077644; PMCID: PMC9455040. The authors could further discuss the role of EZH2 gene mutations in CMML in the light of the above mentioned findings. 4. The therapeutic challenge has to be further analyzed and discussed. A very detailed and informative paper has been recently published by Liapis K et al. (Liapis K, Kotsianidis I. Approaching First-Line Treatment in Patients With Advanced CMML: Hypomethylating Agents or Cytotoxic Treatment? *Front Oncol*. 2021 Dec 13;11:801524. doi: 10.3389/fonc.2021.801524. PMID: 34966690; PMCID: PMC8710500.). 5. In general, one or two of the most updated, relevant and informative references could be added (e.g. Palomo L, Acha P, Solé F. Genetic Aspects of Myelodysplastic/Myeloproliferative Neoplasms. *Cancers* (Basel). 2021 Apr 27;13(9):2120. doi: 10.3390/cancers13092120. PMID: 33925681; PMCID: PMC8124412.). On the other hand, the extended discussion on the 70-year old "field cancerization theory" could be omitted or at last curtailed to the absolutely necessary and educative extent.

## RE-REVIEW REPORT OF REVISED MANUSCRIPT

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**Reviewer's code:** 05430684

**Position:** Peer Reviewer

**Academic degree:** MD, MSc, PhD

**Professional title:** Consultant Physician-Scientist

**Reviewer's Country/Territory:** Greece

**Author's Country/Territory:** China

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**Reviewer chosen by:** Ji-Hong Liu

**Reviewer accepted review:** 2023-04-10 07:10

**Reviewer performed review:** 2023-04-10 07:49

**Review time:** 1 Hour

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer</b>	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous

**statements**Conflicts-of-Interest: [ ☐ ] Yes [ ☒ ] No**SPECIFIC COMMENTS TO AUTHORS**

I studied carefully the revised manuscript entitled "Case report on co-existing squamous cell carcinoma and chronic myelomonocytic leukemia with ASXL1 and EZH2 gene mutations" by Deng L-J et al. The manuscript has been considerably ameliorated after the authors' alterations according to the reviewers' suggestions. Moreover, references have been enriched with some up-to-date and relevant publications. Taken the above mentioned into consideration, the revised manuscript could merit publication.