Peer Review File

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Reviewer A

Comment 1: Method of BRCA mutations analysis (single gene analysis, panel sequencing)? Sequencing of tumor tissue and/or blood DNA?
Reply 1: Next generation sequencing of tumor tissue was conducted using the Foundation One panel.
Changes in the text: We have added this information to lines 86-87 (page 4).

Comment 2: Exact information on the type and location of the BRCA2 mutation (nomenclature according to HGVS); Refseq used.
Reply 2: Unfortunately, this information was not provided by the referring institution and was not available for review by the ITMIG tumor board.
Changes in the text: We have modified our text as advised in lines 87-89 (page 4).

Comment 3: Is the mutation germline or somatic?
Reply 3: Although information on germline testing was not available for review by the ITMIG tumor board, records indicate that the patient's daughter had a similar *BRCA2* mutation, raising the possibility of the presence of a germline mutation.
Changes in the text: This information is now included in lines 89-90 (page 4).

Comment 4: Is there molecular evidence for a second-hit event in the BRCA2 gene?
Reply 4: Unfortunately, this information was not available for review by the ITMIG tumor board.
Changes in the text: We have modified our text as advised in lines 87-89 (page 4).

Reviewer B

Comment 1: The case report article titled "The Therapeutic Relevance of a BRCA2 Mutation in a Patient with Recurrent Thymoma: A Case Report" by Sigurdson et al. incorporates the core key message with necessary details in a concise manner, emphasising the need of publication by the novelty of the case. Adequate literature review pertinent to the case was shown and in the discussion the limitations related to the case has been described. I recommend to accept it as submitted.
Reply 1: Thank you for your review.
Changes in the text: None.

Reviewer C

Comment 1: The authors report a recurrent thymoma with a BRCA2 mutation and discuss the current therapeutic relevance in thymic epithelial tumors (TETs). This manuscript is well-written and informative when considering molecular targeted

therapy for patients with TETs. The reviewer indicates the following points to improve the manuscript.

Major:
Page 2, line 89: please describe the detail of genomic analysis. At least, the following information should be described: 1) what genomic analysis was done, e.g., whole-exome sequencing, genetic panel testing;
Reply 1: The method of mutation analysis was tissue-based (tumor) analysis using the Foundation One panel.
Changes in the text: We have added this information to lines 86-87 (page 4).

Comment 2: 2) the detail of the BRCA2 mutation, i.e., how the nucleic acid sequence was altered. Also, the mutation should be pathogenic;
Reply 2: Unfortunately, these details were not available for review by the ITMIG tumor board.
Changes in the text: We have modified our text as advised in lines 87-89 (page 4).

Comment 3: 3) whether the BRCA2 mutation is germline or somatic. If somatic, the reviewer thinks both alleles should be altered to promote tumorigenesis.
Reply 3: The presence of a similar *BRCA2* mutation in the patient's daughter is suggestive of the presence of a germline mutation.
Changes in the text: This information is included in the revision in lines 89-90 (page 4).

Comment 4: 4) other pathogenic mutations, if found;
Reply 4: Detailed results of genomic analysis by Foundation One were not available for review by the ITMIG tumor board.
Changes in the text: We have modified our text as advised in lines 87-89 (page 4).

Comment 5: 5) tumor mutation burden, if available.
Reply 5: Please see response above.
Changes in the text: We have modified our text as advised in lines 87-89 (page 4).

Comment 6: Minor:
Page 2, line 88: the reviewer understands that the histological review of the recurrent tumor (i.e., type B2 thymoma) was not possible. However, the reviewer is unsure whether the diagnosis of the initial tumor (i.e., type B1 thymoma) was confirmed by the ITMIG tumor board.
Reply 6: No histological review was possible at the ITMIG tumor board, and the initial and recurrent pathology diagnosis were supplied by the presenting physician.
Changes in the text: None.

Comment 7: Page 3, line 118: the reviewer is interested in whether there are any reports on thymoma with a BRCA"1" mutation.
Reply 7: The authors are not aware of any reports describing *BCRA1* mutations in thymomas.

Changes in the text: None.

Comment 8: Page 3, line 121: The side effect of PARP inhibitors (PARPi) is meaningful to mention. Thus, the reviewer suggests describing it more. E.g., 1) what percentages of the patients who received PARPi cause myelodysplastic syndrome/acute myeloid leukemia;
Reply 8: Based on a recent meta-analysis of 28 randomized controlled trials the incidence of myelodysplastic syndrome and acute myeloid leukemia is 0.73% with PARP inhibitor use, compared to 0.47% in placebo groups. Monotherapy with a PARP inhibitor may increase the risk of hematological toxicity.
Changes in the text: We have added this information to lines 120-124 (page 5).

Comment 9: 2) whether this severe side effect is related to any other factors, such as dose, type (or name) of the drugs.
Reply 9: A meta-analysis of 29 randomized controlled trials found the relative risk of high-grade anemia increased with treatment duration longer than 6 months, and the risk was higher with rucaparib and niraparib and ovarian tumor type compared with non-ovarian tumors.
Changes in the text: We have added this information to lines 118-120 (page 5).

Reviewer D

Comment 1: This case report entitled “The Therapeutic Relevance of a BRCA2 Mutation in a Patient with Recurrent Thymoma: A Case Report (MED-22-9-CL-RV8-8380)” by Dr. Sigurdson reported a case of relapsed type B2 thymoma harboring BRCA2 mutation and previously treated with 4 cycles of CAP. The ITMIG cancer board recommended and concluded cytotoxic chemotherapy is optimal and PARP inhibitors will be optional in the later lines of treatment.

Abstract.
1. Background: Chemotherapy is “palliative-intent”. Clarify it in this paragraph.
Reply 1: We agree chemotherapy is palliative-intent and have included this information in the manuscript.
Changes in the text: We have added this information to lines 32 and 106 of the CLEAN version of the edited manuscript.

Comment 2: 2. Case Description:
i. Clarify the subtype of thymoma (A~B3). ii. Clarify the type of chemotherapy. I think “palliative-intent” chemotherapy is in this situation.
Reply 2: We agree this is important information which has been added to the paper.
Changes in the text: We have added this information to lines 32, 37, 38, 81, 85 and 106 of the CLEAN version of the edited manuscript.

Comment 3: Introduction
2nd paragraph: I recommend the authors add the following descriptions (optional).

1. BRCA2 mutation is a possible inherited genetic alteration (variant).
2. Also, BRCA mt increases the risk for occurring cancers.
3. Cancer harboring BRCA mt is sensitive for platinum in general.
Reply 3: This information was added with resultant additional reference.
Changes in the text: We have added this information to lines 67-69 and 90 and new reference number 5 (see lines 169-170).

Comment 4: Case presentation
1. Clarify the family history of cancers in this patient.
Reply 4: We agree this information is very relevant and have added these details to the manuscript.
Changes in the text: We have added this information to lines 89-90 (page 4).

Comment 5: 2. Clarify serum level of IgG, % of reticulocyte, ANA, or anti-ACTH Ab to exclude Good synd., PRCA, SLC, or MG if you have checked.
Reply 5: Unfortunately, antibodies were not tested, and the other bloodwork mentioned was not available for ITMIG to review at the tumor board.
Changes in the text: None.

Comment 6: 3. I recommend authors clarify the assay of BRCA (NGS-based assay?) for readers.
Reply 6: The Foundation One panel was used for genomic analysis of tumor tissue in this case. This information has been added to the manuscript.
Changes in the text: We have added this information to lines 86-87 (page 4).

Comment 7: Discussion
I recommend the authors clarify why volume reduction surgery had not been recommended in this case in the Case presentation or discussion (Did no one recommend it?).
Reply 7: Volume reduction surgery was not considered for treatment of second recurrence due to presence multifocal disease involving bilateral pleurae.
Changes in the text: We have modified our text as advised in lines 129-130 (page 5).

Reviewer E

Comment 1: The authors described a case of recurrent thymoma with a BRCA2 mutation and discussed the relevance of the BRCA2 mutation to treatment with a PARP inhibitor. This case report has the following problems.

1. No resected sample was available for histological review, and no histology images are provided in this manuscript.
Reply 1: Unfortunately, this is true, and we detail this limitation in our case report in lines 85-86 on page 3.
Changes in the text: None.

Comment 2: 2. Detailed information on BRCA2 mutations is lacking. This includes the method and sample (tumor or blood sample) used to identify the mutation, the type of mutation, and the pathogenicity of the mutation.
Reply 2: DNA based next-generation sequencing of tumor tissue was conducted using the Foundation One panel. Unfortunately, details regarding the type of mutation and its pathogenicity was not available for review by the ITMIG tumor board. Although information on germline mutation status was not available, we can infer the presence of a germline mutation due to detection of a similar mutation in the patient's daughter.
Changes in the text: We have added this information to lines 86-90 (page 4).

Comment 3: 3. This patient was not treated with a PARP inhibitor.
Reply 3: We agree this is the case for reasons discussed in lines 130-137 on page 5.
Changes in the text: None.