



# The therapeutic relevance of a *BRCA2* mutation in a patient with recurrent thymoma: a case report

Samantha Sigurdson<sup>1</sup>, Edith M. Marom<sup>2</sup>, Andreas Rimner<sup>3</sup>, Annemarie Shepherd<sup>3</sup>, Malgorzata Szolkowska<sup>4</sup>, Anja C. Roden<sup>5</sup>, Mirella Marino<sup>6</sup>, Noriyuki Tomiyama<sup>7</sup>, David Ball<sup>8</sup>, Conrad Falkson<sup>1</sup>, Arun Rajan<sup>9</sup>

<sup>1</sup>Department of Oncology, Queen's University, Cancer Centre of Southeastern Ontario, Kingston, ON, Canada; <sup>2</sup>The Chaim Sheba Medical Center, Affiliated with the Tel Aviv University, Tel Aviv, Israel; <sup>3</sup>Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; <sup>4</sup>Department of Pathology, National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland; <sup>5</sup>Department of Laboratory Medicine and Pathology, Mayo Clinic Rochester, MN, USA; <sup>6</sup>Department of Pathology, IRCCS Regina Elena National Cancer Institute, Rome, Italy; <sup>7</sup>Department of Radiology, Osaka University Graduate School of Medicine, Yamadaoka, Osaka, Japan; <sup>8</sup>Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; <sup>9</sup>Thoracic and Gastrointestinal Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

*Correspondence to:* Samantha Sigurdson. Department of Oncology, Division of Radiation Oncology, 25 King St. W., Kingston, Ontario K7L 5P9, Canada. Email: samantha.sigurdson@queensu.ca.

**Background:** Thymomas are characterized by a low tumor mutation burden and a paucity of actionable mutations. Clinical behavior can vary from relatively indolent to very aggressive and impact survival. Platinum-based chemotherapy is the primary treatment modality for inoperable disease and is palliative in intent. Patients with advanced thymoma frequently experience disease recurrence after frontline therapy. Treatment options for relapsed thymoma are relatively limited. A case of recurrent thymoma harboring a breast cancer gene 2 (*BRCA2*) mutation was presented for multidisciplinary discussion at the International Thymic Malignancy Interest Group (ITMIG) Tumor Board meeting.

**Case Description:** A 63-year-old female presented with Tumor Node Metastasis (TNM) stage I, World Health Organization (WHO) subtype B1 thymoma at diagnosis and underwent surgical resection. First recurrence occurred in the left costophrenic recess and was treated with preoperative external beam radiotherapy (EBRT), surgical excision, and post-operative chemotherapy. Histology was consistent with WHO subtype B2 thymoma and genomic analysis of the resected tumor detected a *BRCA2* mutation. Second recurrence occurred in the mediastinum and bilateral pleurae. Mediastinal disease was treated with EBRT, and the pleural deposits were observed initially. However, upon further progression, the case was discussed at the ITMIG tumor board meeting to determine optimal second line therapy for this patient.

**Conclusions:** A potential role of poly (ADP-ribose) polymerase (PARP) inhibitors versus cytotoxic chemotherapy for treatment of *BRCA2*-mutated recurrent thymoma merits discussion. However, due to the absence of data to support the functional and therapeutic significance of *BRCA2* mutations in patients with thymoma, the potential for severe toxicity associated with PARP inhibitors, and availability of other safe and effective alternatives, other treatment options should be considered. PARP inhibitors can be considered for treatment of *BRCA2*-mutated thymomas as part of a clinical trial or when other treatment options have been exhausted.

**Keywords:** Thymoma; breast cancer gene 2 (*BRCA2*); poly (ADP-ribose) polymerase inhibitor (PARP inhibitor); olaparib; case report

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## Introduction

Thymic epithelial tumors (TETs) refer collectively to a histological spectrum of rare cancers that include thymomas, thymic carcinomas, and thymic neuroendocrine neoplasms. Thymomas have a low tumor mutation burden and actionable genomic alterations are largely absent (1,2). Defects in immune tolerance increase the risk of paraneoplastic autoimmune disease, especially in patients with thymoma (1). Although thymomas can exhibit indolent clinical behavior, patients with advanced disease frequently experience disease relapse with a 10-year cumulative incidence of recurrence of 57% to 71% (1). A limited number of treatment options are available for patients with recurrent thymoma (1). Due to a low frequency of somatic mutations in recurrent thymoma (3), treatment directed toward specific genomic alterations is largely ineffective (1). Somatic mutations in the breast cancer gene 2 (*BRCA2*), a tumor suppressor gene that plays a key role in DNA damage repair, are present in 3% of advanced-stage TETs (3,4). Germline mutations in *BRCA2* increase the risk for multiple types of cancer. Cancers harboring *BRCA* mutations have increased sensitivity to platinum-based chemotherapy agents (5). Poly (ADP-ribose) polymerases (PARPs) are a family of proteins involved in a number of cellular processes, including DNA repair (6). PARP inhibitors are clinically active in cancers harboring *BRCA* mutations, such as breast, ovarian, pancreatic and castrate-resistant prostate carcinomas (6). However, the role of PARP inhibitors in the treatment of *BRCA2*-mutated TETs is unclear. We present the following case of a recurrent thymoma with a *BRCA2* mutation in accordance with the CARE reporting checklist (available at <https://med.amegroups.com/article/view/10.21037/med-22-9/rc>), which was presented at a virtual tumor board meeting of the International Thymic Malignancy Interest Group (ITMIG), an academic society consisting of an international panel of experts representing various medical specialties, and we discuss the potential role of PARP inhibitors versus cytotoxic chemotherapy for treatment.

## Case presentation

A 63-year-old woman with an initial diagnosis of Tumor Node Metastasis (TNM) stage I, World Health Organization (WHO) subtype B1 thymoma experienced disease recurrence in the ipsilateral (left) costophrenic recess 30 months after initial thymectomy. She was treated

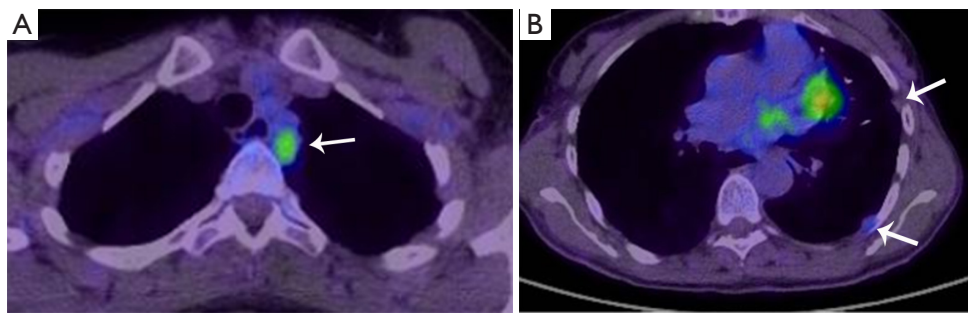
with preoperative external beam radiotherapy (EBRT) to 45 Gy in 15 fractions, followed by pleurectomy, diaphragmatic resection and pericardiectomy for treatment of multiple parietal pleural metastases that were detected at the time of surgery. Histology of the resected tumors was consistent with WHO subtype B2 thymoma. However, the resection sample was not available for histology review at the ITMIG tumor board. Somatostatin receptor scintigraphy was negative. Foundation One next generation sequencing of DNA extracted from the surgical specimen demonstrated the presence of a *BRCA2* mutation. Details about the *BRCA2* mutation, including the variant allele frequency, and information about germline testing for *BRCA2* was not available for review by the ITMIG tumor board. Family history included a sister with breast cancer and a daughter with a similar *BRCA2* mutation, which was suggestive of the patient harboring a germline mutation of *BRCA2*.

Due to microscopically positive surgical margins the patient received four cycles of post-operative chemotherapy (cisplatin, doxorubicin and cyclophosphamide). Eighteen months after surgery, a whole body 18-fluorodeoxyglucose positron emission tomography (FDG-PET)-computed tomography (CT) scan demonstrated FDG-avid recurrent disease (*Figure 1A*), and two small foci of disease in the pleura with low FDG uptake (*Figure 1B*). The patient received EBRT (36 Gy in 12 daily fractions) for treatment of disease abutting the mediastinum and the pleural deposits were monitored. Four months after the second course of EBRT, a chest CT scan demonstrated multifocal disease progression involving the left and right pleurae, with the appearance of multiple new pleural metastases (*Figure 2A,2B*). There was no evidence of recurrence within the previously irradiated pleura of the left costophrenic recess or development of extra-thoracic metastases.

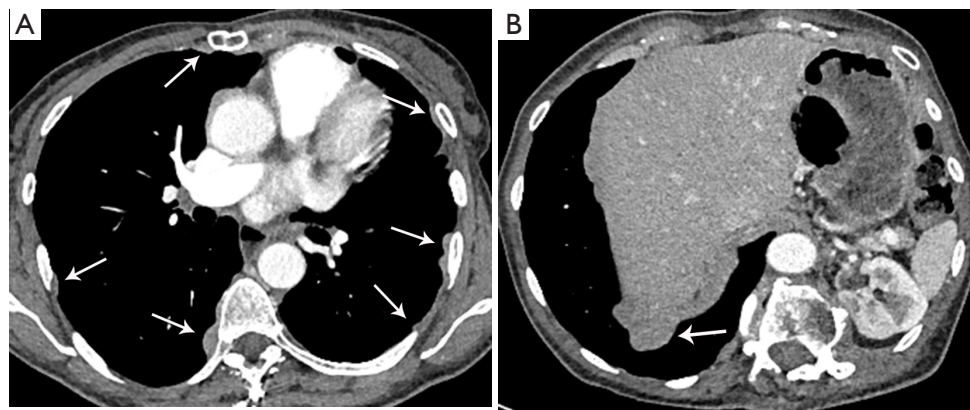
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and the accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

## Discussion

Treatment options for recurrent thymoma include cytotoxic chemotherapy with drugs such as pemetrexed, gemcitabine,



**Figure 1** Fused FDG-PET-CT scan eighteen months after initial surgery, demonstrates (A) FDG-avid recurrent disease at the border of the mediastinum and left pleura (arrow), and (B) two additional smaller mildly FDG-avid left pleural deposits (arrows). FDG-PET, 18-fluorodeoxyglucose positron emission tomography; CT, computed tomography.



**Figure 2** Contrast enhanced chest CT (soft tissue windows) obtained five months after imaging shown in (A) reveals too numerous to count new bilateral pleural nodules (arrows), consistent with progressive bilateral pleural metastatic disease, and (B) larger volume of pleural metastatic involvement in the right pleura inferiorly (arrow) with no recurrence within the previously irradiated pleura of the left costophrenic recess. CT, computed tomography.

capecitabine and taxanes, targeted therapy with the mammalian target of rapamycin inhibitor, everolimus, somatostatin analogs with or without prednisone for tumors showing uptake on somatostatin receptor scintigraphy, and participation in clinical trials, when available (1). Pemetrexed is frequently used for second-line treatment of thymoma due to its ability to induce durable responses and its excellent safety profile (7). Treatment of unresectable or recurrent disease is palliative in nature.

Somatic mutations in *BRCA2* have been observed in 3% of advanced-stage TETs (3). However, the functional and clinical significance of these mutations is unclear and the role of PARP inhibitors for the treatment of recurrent TETs is not clearly established. To our knowledge there is only one case reported in the literature of a patient

with recurrent thymoma harboring a germline frameshift mutation in *BRCA2* who experienced durable disease stabilization with the PARP inhibitor, olaparib (8). Of note, the patient had received multiple systemic therapies previously over a 10-year period with intervals of disease stability, including a two-year period while receiving an insulin-like growth factor-1 receptor inhibitor, which raises the question of the role of intrinsic tumor biology in disease stabilization rather than the effect of PARP inhibition. Recent research has also uncovered the effect of PARPs on innate and adaptive immunity as well as the tumor microenvironment (9,10). It is unclear if the immunomodulatory effects of PARP inhibition rather than synthetic lethality in the presence of an underlying *BRCA2* mutation contributed to tumor control in the previously

published case report.

Treatment with PARP inhibitors can cause clinically significant adverse events, including severe hematological toxicity (11). High-grade anemia was associated with treatment duration longer than 6 months, treatment with rucaparib or niraparib, and underlying ovarian cancer (11). More concerning, an increase in the risk of myelodysplastic syndrome and acute myeloid leukemia has been described in patients treated with PARP inhibitors (12). A recent meta-analysis found a small, but increased risk of developing myelodysplastic syndrome and acute myeloid leukemia in association with PARP inhibitor therapy compared with placebo with an odds ratio of 2.63 (absolute difference in incidence: 0.73% versus 0.47%) (12). Hence, a careful assessment of potential risks and benefits is essential while considering the use of PARP inhibitors for treatment of *BRCA2*-mutated recurrent thymoma.

The ITMIG panel was asked for input on the optimal choice for second-line systemic therapy in a patient with a *BRCA2*-mutated recurrent thymoma who has previously received platinum-based combination chemotherapy, and if a PARP inhibitor is indicated due to the presence of the *BRCA2* mutation. Volume reduction surgery was not considered for treatment of second recurrence due to presence multifocal disease involving bilateral pleurae. In the absence of data to support the functional and therapeutic significance of *BRCA2* mutations in patients with thymoma, the potential for severe toxicity associated with PARP inhibitors, and the availability of other safe and effective treatment options, the ITMIG panel recommended the use of pemetrexed in this case for second-line treatment of recurrent thymoma and suggested that PARP inhibitors should be considered for treatment of *BRCA2*-mutated thymomas only as part of a clinical trial or if other treatment options have been exhausted. Further research is needed to define the role of PARP inhibitors in TETs with mutations involving DNA damage and repair genes, including *BRCA2* mutations.

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The patient involved in this case report provided her informed consent authorizing use and disclosure of her health information.

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## Footnote

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**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and the accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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