International Journal of Biomedicine 13(4) (2023) 380-384
http://dx.doi.org/10.21103/Article13(4)_CR5

CASE REPORT

INTERNATIONAL JOURNAL OF BIOMEDICINE

A Rare Case Resistant Chemotherapy Thymoma B2 Type, New Approach

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Abstract

Invasive thymomas and thymic carcinomas are relatively rare tumors, which together represent about 0.2% to 1.5% of all malignancies. The majority of thymomas (90%) are found in the anterosuperior mediastinum. Type B2 thymoma, one of the rarest cases, was diagnosed in a 35-year-old male. Anamnesis, imaging examination, serological and invasive procedures confirmed the diagnosis. In 2020, the patient was operated on with thymoma R0-resection. The patient showed no progression until July 2022, when a locoregional recurrence was detected. The patient received 6 cycles of chemotherapy, to which the tumor showed resistance. After 6 months, the patient started a treatment with tyrosine kinase inhibitor sunitinib. If a patient is diagnosed with thymoma B2 that does not respond to standard chemotherapy, the tumor can be accepted as an aggressive one requiring a change to a new treatment.**(International Journal of Biomedicine. 2023;13(4):380-384.)**

Keywords: thymoma • diagnosis • treatment • outcome

For citation: Çmega VG, Jakupi A, Agaj A. A Rare Case Resistant Chemotherapy Thymoma B2 Type, New Approach. International Journal of Biomedicine. 2023;13(4):380-384. doi:10.21103/Article13(4)_CR5

Introduction

Thymomas originate from the thymic epithelial cells within the anterior mediastinum but can be found in the posterior and middle mediastinum or neck.[1] Thymomas are associated with an exuberant lymphoid component composed of immature cortical thymocytes. Different thymoma types exhibit different patterns of thymopoiesis, and type B thymomas produce more lymphocytes than type A.[2] Thymomas are exceedingly rare. The Surveillance, Epidemiology, and End Results (SEER) Program showed a thymoma incidence of 0.15 per 100,000 person-years. The incidence was higher in males than females (P=0.007).[3] Thymomas are generally characterized by an indolent growth pattern that can be locally invasive. Thymomas are intimately associated with a wide spectrum of immunological diseases. Type B thymomas are most often associated with immune disorders. Myasthenia gravis is the most common immune-mediated disease associated with thymoma, and 30%-40% of thymoma patients suffer from myasthenia gravis.[4,5]

Case Presentation

In July 2020, a 35-year-old male patient felt symptoms of cough, chest pain, and dyspnea. After many laboratory and radiological examinations (Fig.1), the patient was found to have a mediastinal mass in the anterior mediastinum.

Later, the surgery was performed with total resection of the mass described in the pathohistological report as R0 resected margins type B2 thymoma. At that time, the patient did not receive any treatment. After 2 years, in June 2022, the patient was given another chest examination where the locoregional recurrence had been detected, along with enlarged lymph nodes in the neck (Fig.2). A second biopsy was done, and it resulted in the same pathohistological diagnosis: Thymoma B2 type (cortical thymoma), an invasive malignant subtype. The therapy included 6 cycles of chemotherapy (carboplatin, doxorubicin, cyclophosphamide), starting on 07/29/2022, with the last cycle on 11/15/2022. On CT examinations performed on 11/17/2022, the findings were compared to the examinations before treatment: Left para-aortic mass with dimensions of 1.4 cm without changes in dimensions, the subpleural mass at the 8th posterolateral rib (3.6×2.0 cm in the previous examination with current dimensions of 3.2×1.8 cm), left subpleural infiltration 3.7×1.7 cm in the last examination with current dimensions of 3.4×2.1cm. Infiltrative left paravertebral mass of 1.3×4.0 cm versus 1.8×4.5 cm before treatment. Left posterobasal pleural thickening. No metastases have been seen in the abdomen during all those years.

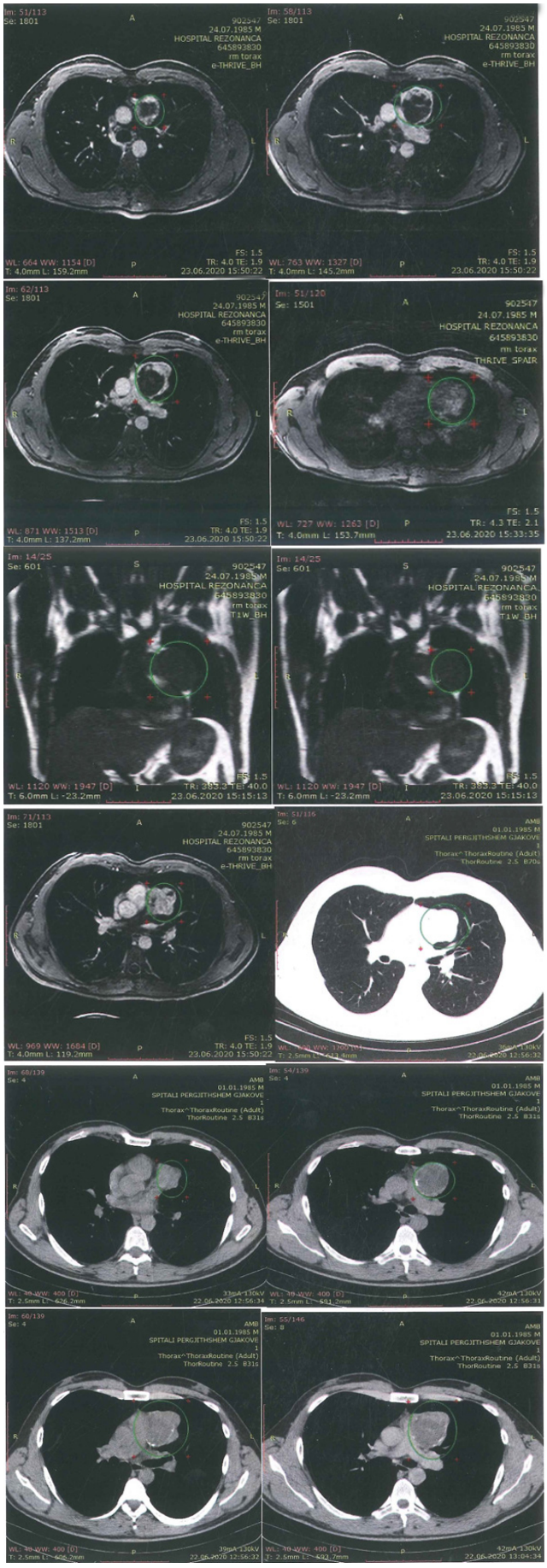

Fig. 1. *June 2020: Thorax MRI and CT before operation.*

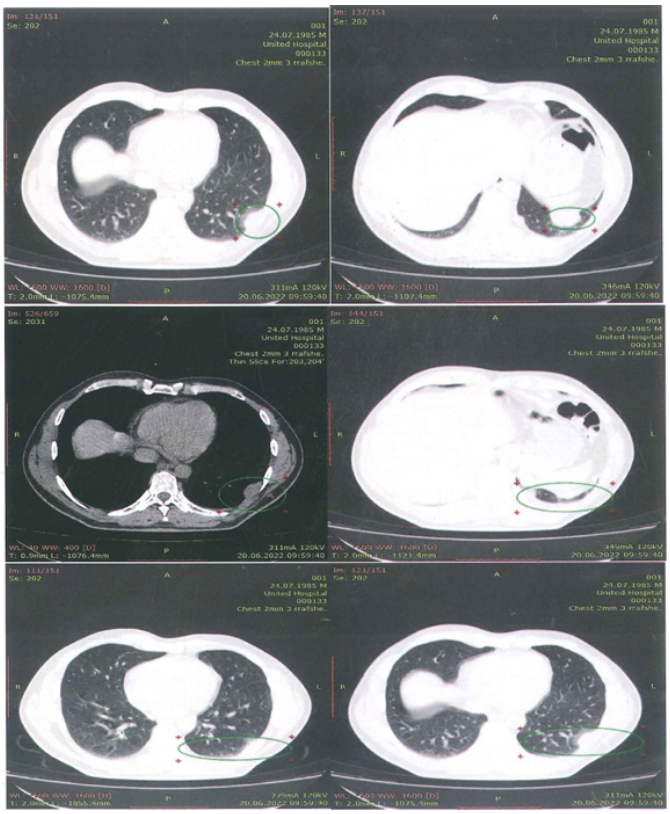

Fig. 2. *June 2022: Thorax CT before operation.*

Echocardiography (09/19/2022): LVEF-70%. Data from a large panel of tumor markers, as well as laboratory and biochemistry analysis, were in normal values before and after chemotherapy. In the biochemistry analysis on 05/09/2023, cholesterol was 7.4 mmol/l, and triglycerides - 2.69 mmol/l.

Chest CT on 05/22/2023: minimal left interlobar pleural effusion, contrast-enhancing solid mass about 70×30mm adhering to the thoracic wall in the mediastinum. Progression was detected in the radiological evaluation, performed in December 2022 (Figure 3).

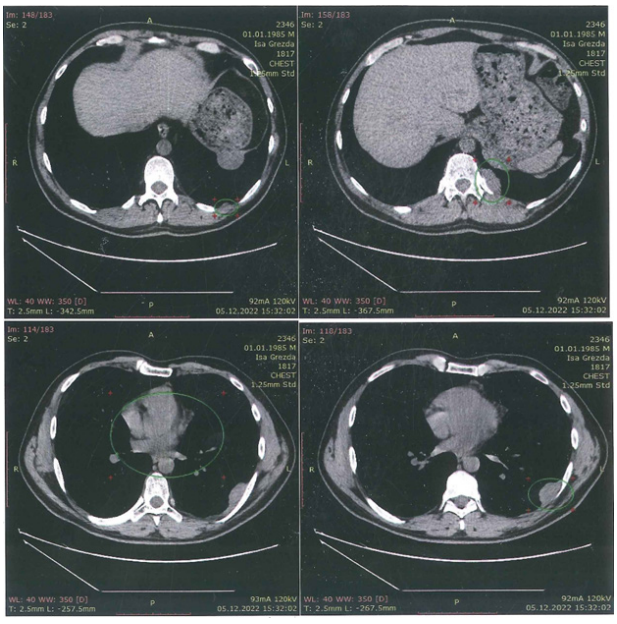

Fig. 3. *December 2022: Thorax CT after operation.*

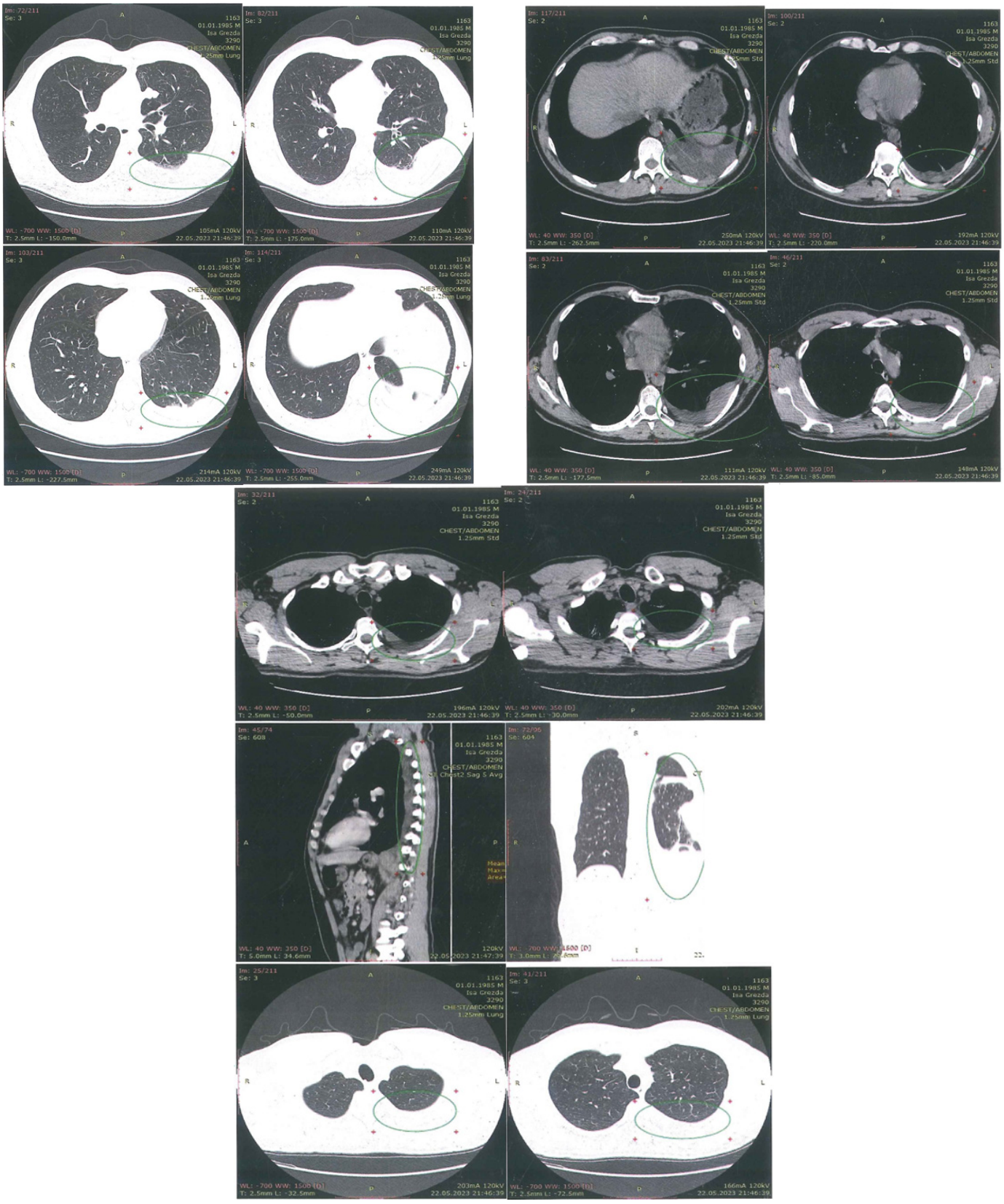

Fig. 4. *May 2023: Thorax CT after chemotherapy.*

Afterward, the patient was not treated with any kind of specific oncological therapy. On the patient's chest CT (May 2023), prominent pleural effusion and pleural mass were detected on his left side (Figure 4). The patient had no accompanying paraneoplastic syndrome findings and has started with sunitinib (Sutent) (50 mg daily for 28 days, followed by a 14-day break; this is 1 cycle of treatment). The patient was recommended to do a PD-L 1 testing, considering therapy with pembrolizumab added to carboplatin and paclitaxel for future treatment, because the patient did not have any autoimmune findings.

Discussion

The vast majority of thymomas are cytologically bland tumors, and approximately half of them are noninvasive.[6-10] Roughly one-third are asymptomatic and found incidentally on a chest X-ray.[11,12] Of those with symptoms, 40% have symptoms relating to impingement by the intrathoracic mass, ranging from cough, chest pain, dyspnea, hoarseness, super vena cava obstruction, and even tumor hemorrhage.[13] Another 30% of those with symptoms have systemic signs, and the remainder present with signs of myasthenia gravis. Most thymomas are indolent, but if the tumors spread, they most commonly implant regionally on the pleural surfaces and can cause pleural plaques, diaphragmatic masses, and malignant pleural effusion. Thymomas have been extensively studied by pathologists. Many different classification systems have been proposed and used. The major distinction has been described as noninvasive thymomas versus invasive or, alternately, benign versus malignant. Even bland-appearing, noninvasive thymomas have fundamental characteristics of a malignant tumor in the ability to recur and metastasize.

According to the WHO classification, thymic epithelial tumors are classified into thymomas (types A, AB, B1, B2, and B3) and thymic carcinomas, based on the morphology of epithelial cells and the ratio of lymphocyte-to-epithelial cells.[14] Type B2 thymoma is characterized by increased numbers of single or clustered polygonal or dendritic epithelial cells intermingled with abundant immature T cells. Tumor cells tend to palisade around blood vessels and fibrous septa. Enlarged perivascular spaces are often found.[15]

Among factors that affect the prognosis and treatment options of thymomas, the invasiveness and completeness of resection should be highlighted.[6,7] A large multi-institutional survey from Japan reported 5-year survival rates in 1,320 patients of 100%, 98.4%, 88.7%, 70.6%, and 52.8% for Masaoka stages I, II, III, IVa, and IVb, respectively.[16] In a study by Cowen et al.,[17] 10-year disease-free survival rates were 92%, 87%, 60%, and 35% for stages 1, II, Ill, and IV, respectively. In a study by Regnard et al.,[18] 15-year disease-free survival rates for stages I, Il, II, and IV were 78%, 73%, 30%, and 8%, respectively.

The extent of resection is the other major prognostic factor. Patients with an R0 resection have significantly improved survival over those with R1 or R2 resections. While an R0 resection is almost always accomplished in stage I tumors, resectability rates decrease on average to 50% in stage III tumors.

Some studies have suggested that tumor size also may be a prognostic factor in thymoma.[19] Bian et al.[20] analyzed the SEER database and found that tumor size was associated with postoperative disease-specific survival and overall survival. Fukui et al.[21] found that tumor size >4cm was an independent prognostic factor for recurrence-free survival. In a study by Okumura et al.,[22] the 10-year recurrence-free survival rate was 93.8% in patients with a tumor ≤5.0 cm and 84.3% in patients with a tumor >5.0 cm (P<0.0001).

Age also has been suggested as a prognostic factor. Patients younger than 30 to 40 have a better prognosis.[17,23]

General management

Surgical resection is the mainstay of treatment for thymomas. A complete block surgical resection (RO) remains the treatment of choice for all thymomas regardless of invasiveness, except in rare, advanced cases with extensive intrathoracic or extrathoracic metastasis. Fortunately, the vast majority (90% to 95%) of thymomas are localized. Operative mortality averages 2.5% (0.7% to 4.9%).[18,24-27]

Because the completeness of resection is such an important prognostic factor, an aggressive surgical approach is justified to remove as much of the lesion as possible at the time of surgery. R1 represents a patient who has undergone tumor resection but still has residual microscopic disease present.

Although with total surgical resection, a five-year survival rate of 60% has been reported, the long-term prognosis is poor and depends on the progression of the disease and the degree of tumor differentiation.

The overwhelming recurrence pattern for thymomas is locoregional. Eighty-one percent of recurrences are local, 9% distant, and 11% both.[18,25-28]) Most recurrences arise within 3 to 7 years.[18,24,27,28] Maggi et al.[24] reported clinical and histopathological aspects of 241 thymomas that were reviewed. Radical resection was performed in 87.5% of the patients, subtotal resection with residual tumor in 8.7%, and simple biopsy in 3.7%. A tumor relapse was observed in 24(10%) patients: 2(1.5%) of 133 with encapsulated thymomas and 22(20.4%) of 108 with invasive thymomas.

Thymomas have proven to be very sensitive to chemotherapy. A clinical response is seen in roughly two-thirds of patients. Complete responses are seen about a third of the time. The commonly employed drugs in combination chemotherapy are cisplatin, doxorubicin, and cyclophosphamide. One prospective intergroup study reported disappointing results with combined etoposide, ifosfamide, and cisplatin.

Targeted drugs such as tyrosine kinase inhibitors and mammalian target of rapamycin (mTOR) inhibitors are targeted therapies used in the treatment of thymoma and thymic carcinoma. Tyrosine kinase inhibitors block signals needed for tumors to grow. mTOR inhibitors block a protein called mTOR, which may keep cancer cells from growing and prevent the growth of new blood vessels that tumors need to grow. To treat recurrent thymoma or recurrent thymic carcinoma, tyrosine kinase inhibitors sunitinib or lenvatinib and mTOR inhibitor everolimus may be used.

In conclusion, for thymoma management, a multimodal approach is recommended, including surgical resection, postoperative radiation, chemotherapy, and target therapy. Specific targeted therapy for treating thymic malignancies has shown promising results in some small clinical studies. The prognosis of thymic carcinoma is poor due to the early involvement of the lymph nodes pleura, lungs, mediastinum, cervical and axillary lymph nodes, brain, bone, and liver metastasis. Median survival and disease-free survival are very encouraging when molecular therapy is integrated into cytostatic treatment. Type B2 thymoma, known as cortical or polygonal cell thymoma, can be considered an invasive malignant tumor.

Competing Interests

The authors declare that they have no competing interests.

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