Letter to the Editor

ITMIG 2021 Tumor Board: a case of a 37-year-old man with TNM stage IVA thymoma

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Case presentation

At the 11th International Thymic Malignancy Interest Group Annual Meeting, a multidisciplinary expert panel discussed the diagnosis and treatment strategies of a 37-year-old man with TNM IVA type B2B3 thymoma.

Due to pain in the right shoulder and lower chest the patient underwent chest computed tomography (CT) that revealed a right mediastinal mass and right nodular pleural thickening. Video-assisted thoracoscopic surgery (VATS) biopsy of the mass showed a thymoma (the radiological and histopathological reports from that period were unavailable to the expert panel—the diagnostics was performed at another institution). The patient received six courses of chemotherapy (CAP regimen: Cisplatin, Doxorubicin, Cyclophosphamide). The positron emission tomography (PET)/CT performed after chemotherapy did not reveal significant regression of the tumor with an ^{18}F-fluorodeoxyglucose (FDG)-avid 6.5 cm right mediastinal mass invading the right lung and FDG-avid nodular right pleural metastases (*Figure 1*).

The patient contacted a center with extensive experience in the treatment of thymomas and underwent surgery through a right thoracotomy five months after chemotherapy. All neoplastic lesions from the mediastinum, the diaphragm and the lung were removed (non-anatomical resections). The pathological diagnosis of a WHO type B2B3 thymoma, TNM stage ypT3N0M1a (IVA) was established (1,2). The resection was microscopically considered incomplete (*Figure 2*).

Four months later a new PET/CT showed an FDG-avid 1.5 cm recurrence in the right anterolateral lower chest wall (*Figure 3*) that was resected a month later. Microscopic analysis revealed a tumor of similar histology and positive resection margins (*Figure 4*). After surgery the patient was given three cycles of chemotherapy (Cisplatin, Ifosfamid, Etoposid).

Fifteen months after the second surgery a chest CT revealed tumor recurrence in the right mediastinal pleura and right anterior diaphragmatic space and a right upper lung lobe metastasis (*Figure 5*). The patient underwent right re-thoracotomy with resection of multiple lesions from the chest wall, diaphragm (resections and reconstructions), mediastinum, right pulmonary hilum and right lung (non-anatomical resections).

A chest CT three months later showed a 3 cm recurrence in the right anterior diaphragmatic space (*Figure 6*), which was removed via a subxiphoid approach.

Three cycles of chemotherapy (Carboplatin, Paclitaxel) were given. The most recent chest CT four months after the last surgery showed no signs of recurrence but revealed a paralyzed right diaphragm.

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

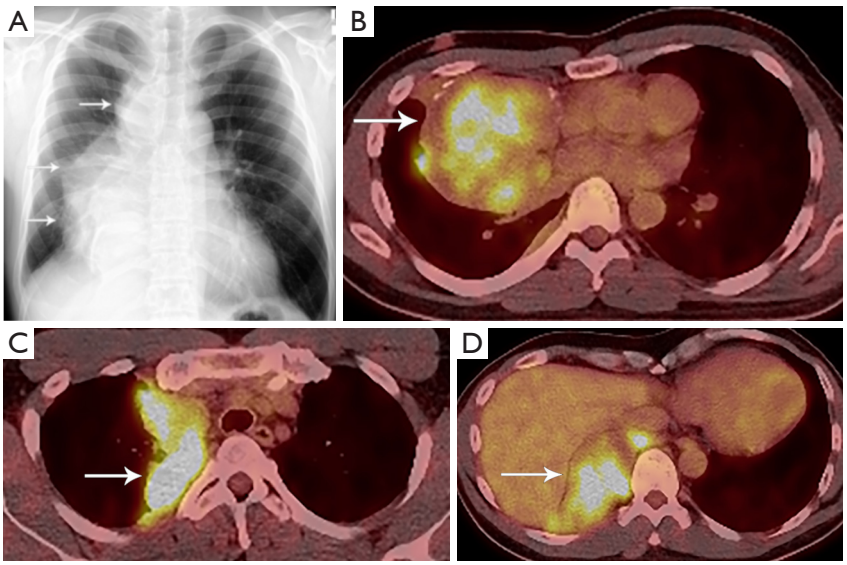

Figure 1 Chest radiograph and PET/CT of the primary tumor. (A) Frontal chest radiograph shows a large right prevascular (anterior) mediastinal mass (arrows). (B-D) Axial PET/CT shows an FDG avid right prevascular (anterior) mediastinal mass (arrow) extending into the lung (B) with nodular right pleural thickening involving the right mediastinal pleura (arrow) in the upper right hemithorax (C) and the diaphragmatic pleura (arrow) (D) consistent with right pleural metastases. PET-CT, positron emission tomography-computed tomography; FDG, fluorodeoxyglucose.

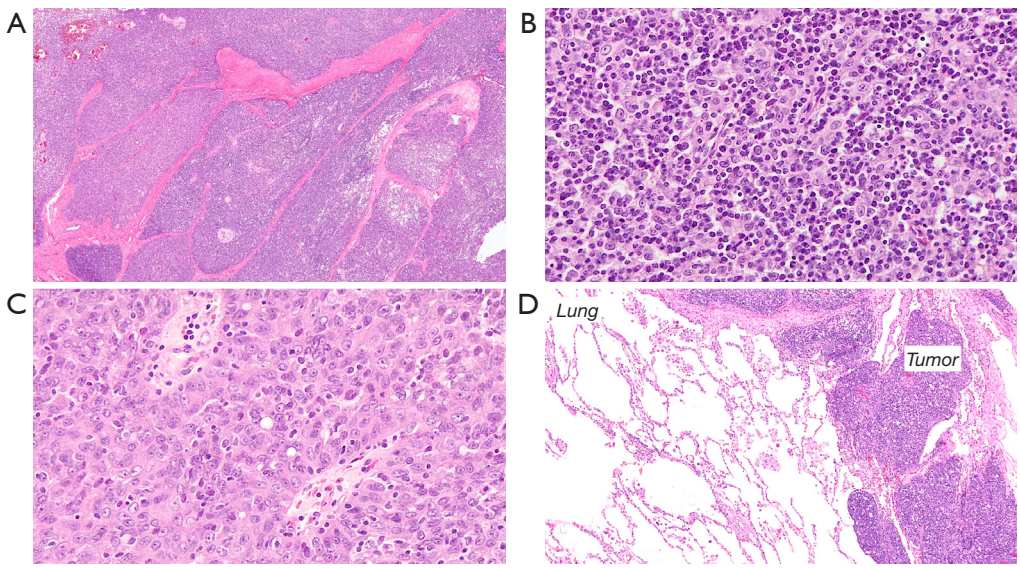

Figure 2 Morphology of the primary tumor after neoadjuvant therapy. The resection specimen included an 18×11×6 cm mediastinal mass, a 12×9×4 cm diaphragmatic parietal tumor, a 10×9×4 cm visceral pleural tumor and a 2.5×2×1.5 cm paravertebral tumor. All tumors available for review (mediastinal mass, visceral pleural tumor, and paravertebral tumor) showed lobulated cellular neoplasms that were at least focally encapsulated. The cellular lobules were intersected by fibrous bands (A). While in some areas there was a mixture of thymocytes and polygonal tumor cells which focally clustered, other areas were characterized by sheets of large polygonal tumor cells with only a few scattered thymocytes. These morphologic features were characteristic of types B2 (B) and B3 (C) thymoma, respectively. The thymoma in the visceral pleura focally invaded into the lung parenchyma (D). The paravertebral tumor showed a cauterized margin that was involved by the thymoma. No definite treatment response was identified in any of the tumors. Based on the available information the tumor stage was ypT3N0M1a and it was considered an incomplete (R1) resection (HE stain, magnification: A: ×20, B-C: ×200, D: ×40).

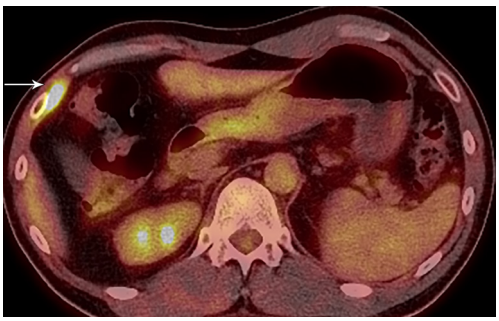

Figure 3 PET/CT—the first recurrence. Axial PET/CT demonstrates FDG avid tumor recurrence in the right anterolateral lower chest wall involving the right diaphragmatic pleura (arrow). PET-CT, positron emission tomography-computed tomography; FDG, fluorodeoxyglucose.

and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Surgeon's comments

Right thoracotomy following induction chemotherapy chosen for the initial resection of the tumor seemed to provide better access compared to a median sternotomy. The advantage of a right thoracotomy is a better view and control of pleural implants, especially along the diaphragm and deep in the costo-vertebral sulcus. Moreover, by avoiding a sternotomy, the risk of tumor spillage into the left (i.e., contralateral) pleural cavity is reduced.

However, one could also consider a right extrapleural

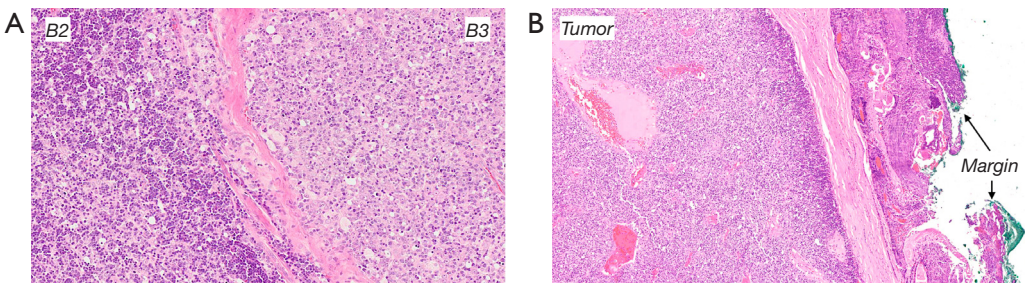

Figure 4 Histology of the first recurrence. (A,B) The microscopic slides from the 1st recurrence (tumor from the right 7th intercostal space) showed morphological features of type B2 and B3 thymoma similar to the primary tumor (A) and also revealed a positive margin consistent with an R1 resection (B). While no slides were available from the 2nd recurrence (which was also described as B2 and B3 thymoma), the slides from the 3rd recurrence showed again morphological features of types B2 and B3 thymoma (not shown) (HE stain, magnification: E: ×100, F: ×40).

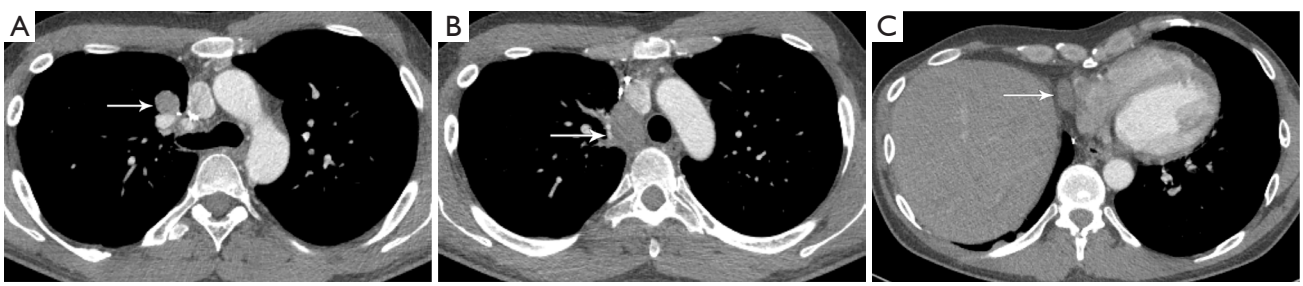

Figure 5 Chest CT—the second recurrence. (A-C) Contrast enhanced chest CT reveals right upper lung metastasis (arrow) contiguous with the right hilum (A), and tumor recurrence in the right mediastinal pleura (arrow) in the paratracheal region (B) and right anterior diaphragmatic space (arrow) (C). CT, computed tomography.

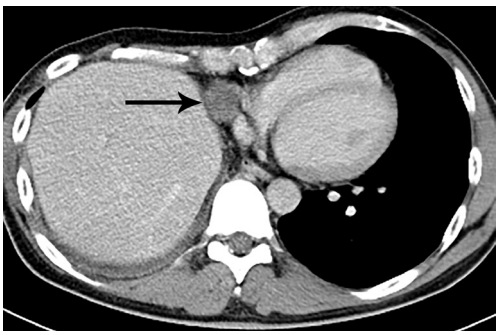

Figure 6 The third recurrence. Contrast enhanced CT shows recurrence in the right anterior diaphragmatic space (arrow). CT, computed tomography.

pneumonectomy (EPP) as the initial operation rather than repeated non-anatomical resections sparing lung parenchyma (3-5). EPP might result in fewer local recurrences, but concurrently might reduce the chances for future surgical resections in case of a local pleural recurrence. This might require local radiation treatment (RT) for disease control later in the course of the disease.

The presented approach resulted so far in a successful outcome with apparently no evidence for residual disease three years after initial presentation and following multiple surgical interventions to achieve local control of the recurrent malignant thymic disease.

Radiation oncologist's comments

There is no indication for this patient to receive (RT) at present time.

RT is predominantly used after surgery to reduce the risk of mediastinal relapse. RT can be used as a part of definitive treatment for patients who are not operable or for tumors that are not resectable after preoperative chemotherapy or for patients who are unable to tolerate the preoperative chemotherapy.

As most patients have disease confined to the thorax, RT fields often encompass one or more thoracic structures (mediastinum, pleura and, occasionally, pericardium) and is typically performed with the aim of local control and tumor eradication. For recurrent disease the doses may vary, e.g., lower doses aimed at symptoms control, while higher doses may be employed for definitive treatment (6-9). Clear statement of the clinical goal and of the area treated with radiation is needed.

Generally, patients with thymoma live long enough to manifest late side effects due to treatment. This patient has a paralyzed right diaphragm, which might compromise his respiratory and digestive systems. He needs to be followed very carefully for further recurrence and any side effects of chemotherapy he has received (10).

Medical oncologist's comments

The probability of cure for a patient with stage IVA thymoma with surgery and chemotherapy is relatively low. There is some controversy about the role of aggressive surgical debulking. If a surgical approach is chosen then neoadjuvant chemotherapy is usually recommended, and the three-drug regimen CAP (Cisplatin, Doxorubicin, Cyclophosphamide) is frequently selected due to the high response rate and relative tolerability. In the presented case the tumor did not have a robust initial response to chemotherapy. Adjuvant chemotherapy after aggressive surgery is controversial and usually not recommended (11).

The second regimen chosen for this patient after initial recurrence, Ifosfamide, Cisplatin and Etoposide, is another aggressive combination regimen that has a high response rate. The extended period of time (well over a year) from completion of chemotherapy and the next recurrence implies some response. When the disease recurred again, the patient received Carboplatin and Paclitaxel, another known active regimen.

The risk of further progression in this patient is high (12). In case of the next recurrence, it seems reasonable to repeat the last drug regimen (carboplatin/paclitaxel) assuming there has been a long enough disease free interval to justify such an approach. Other possible therapies include the mechanistic target of rapamycin (mTOR) inhibitor—everolimus, or other chemotherapy options including pemetrexed, platinum/etoposide (the most active components of the prior regimen that led to the longest disease free interval), or gemcitabine based regimens (11). Immune checkpoint inhibitor based regimens in this patient with thymoma should be avoided given the high risk of autoimmune toxicity, but many cytotoxic chemotherapeutics have activity in thymoma. Multi-targeted tyrosine kinases inhibitors have also been utilized, though with more efficacy in thymic carcinoma than thymoma.

Systemic therapy would be the most likely next therapy, however, though more controversial, if the next recurrence was limited to the pleura there would also be some consideration for further resection followed by hyperthermic intrathoracic chemotherapy. This technique is available at

limited centers, and though the data to support this approach are minimal and only retrospective, there have been some case studies with encouraging long term survival (13,14).

Conclusions

The presented case illustrates how complex and challenging the treatment of advanced thymic tumors can be and why the high stage cases require a multidisciplinary discussion.

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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 and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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