

A Large Thymoma Resected *via* Left Antero-lateral Thoracotomy

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Abstract. *Background/Aim:* Thymomas are a rare type of mediastinal tumors with a slow growth rate. Because of this, they are well tolerated and patients usually present with large masses, which can extend in either of the thoracic cavities. The surgical approach for such tumors is dictated by the size and localization of the mass. *Case Report:* We present the case of a patient with a large thymoma, resected through surgery performed by left antero-lateral thoracotomy. The patient presented in our clinic with a persistent cough, dyspnea, chest pain and tightness. Standard

thoracic X-ray revealed a bilateral increase in size of the mediastinal shadow, mainly on the left side, with well-defined margins and subcostal intensity. A thoracic computed tomography (CT) scan discovered a tumoral mass within the antero-superior mediastinum, with compression of the mediastinal organs; presentation being suggestive for a thymoma. Surgery was performed, removing a 15/13/10 cm thymoma with a weight of 1126 g. Pathological examination as well as immunohistochemistry confirmed our diagnosis of type AB thymoma, stage I Masaoka–Koga. *Conclusion:* In conclusion, surgical treatment remains the main therapeutic option in thymomas, but it is often difficult to perform due to tumor size and local invasion. However, even in large thymomas of stages I and II, surgery can be performed using an antero-lateral thoracotomy.

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Thymomas are rare tumors and, along with thymic carcinomas, make up the epithelial tumors originating in the thymus. Literature states that thymomas, out of the entire mediastinal masses, have an incidence of 20-30% in adults and only 1% in children (1, 2). Thymomas, although rare, represent the most frequent type of anterior mediastinal mass (50% of cases) (3). According to some authors, the incidence

of thymomas is 2.5/1,000,000 people/year with a median age between 50 and 60 years and an even distribution between genders (4), while other authors have stated an incidence rate of 0.13-0.15/100,000 people/year (3). Thymomas are more frequent in the Asian population and Pacific islanders, followed by black people and then Caucasians. This indicates that genetics may be a part in the development of this disease (4). Also, smoking and spirits consumption are a risk factor (5).

Other studies claim that radiation exposure or aging are linked to thymomas (5). The most recent classification of thymomas (2015) according to World Health Organization (WHO), separates thymomas in several types: A, AB, B1, B2, B3 and type C – thymic carcinoma. Types AB and B2 are the most frequent types of thymoma found in patients (6) and also, the mixed pattern is the most commonly found, appearing in 10% of cases (7). Another type of thymoma are neuroendocrine thymic tumors, which represent 2% of thymic tumors. According to some authors, neuroendocrine thymic tumors have an incidence of 1/5,000,000 people/year (8). Thymoma staging was established using the system developed by Masaoka in 1981 and completed by Koga in 1994. The aim of this study is to present a case of a large thymoma resected using an antero-lateral thoracotomy.

Case Report

We present the case of a 67-year-old male, non-smoker. He presented in our clinic for a persistent cough accentuated by dorsal decubitus position, thoracic pain and retrosternal pressure, dyspnea, physical weakness, loss of appetite and weight loss of 1 kg in the previous month. The patient noticed the symptoms in the last three weeks before admission. Blood tests revealed mild anemia, hemoglobin (Hb) 10.5 g/dl, with a slightly elevated partial pressure of carbon dioxide (pCO₂). Biochemical and coagulation profiles were within normal limits. Antero-posterior chest x-ray revealed an increase in size of the mediastinal shadow in both hemithoraces, more accentuated towards the left hemithorax, with well-defined margins of subcostal intensity, suggesting the presence of a mediastinal mass. There was also a minimal pleural effusion in the cardio-diaphragmatic sinus.

A standard and contrast thoracic computed tomography (CT) scan (Figure 1) confirmed an encapsulated tumor of 139/123/105 mm with well-defined margins, located in the antero-superior mediastinum, developing more towards the left hemithorax. The mass was hyperdense, with central hypodense areas suggesting necrosis and compression of the trachea, esophagus, ascending aorta, aortic arch, left pulmonary artery, heart and left lung, with no invasion of these structures. No bronchial or vascular obstruction by compression was observed. Lymph nodes were of 14 mm maximum size, located in the left hilum, paraaortic and

subaortic. The CT aspect was suggestive of an anterior mediastinal mass, possibly thymoma. Respiratory volume tests revealed a slightly diminished forced expiratory volume (FEV1) and vital capacity (VC), while both electrocardiogram (EKG) and echocardiography were within normal limits, with no significant modifications.

Surgery was performed by left antero-lateral thoracotomy through the fourth intercostal space due to the growth of the mass in the left hemithorax. Intraoperatively, we discovered a well-defined encapsulated tumor, with no invasion in the adjacent anatomical structures (Figure 2). After the incision of the mediastinal pleura, we noticed tight adhesions between the mass and the phrenic nerve and, after separating it, we moved on towards the left pulmonary hilum, where similar adhesions were present between the tumor and the left pulmonary artery, aortic arch and the left brachiocephalic artery. The left innominate vein was very difficult to dissect due to adhesions, especially at the confluence point with the superior vena cava. On the right side, due to reduced visibility, dissection was very difficult. After detaching the tumor from the pericardium posteriorly and from the antero-inferior mediastinal fat we removed the tumor which weighed 1226 g and was 15/13/10 cm. The patient had a favorable postoperative evolution, with no complications and was discharged after seven days of hospital care.

Pathological examination revealed a tumor mass (Figure 3) with a nodular architecture, with nodules being separated by thick bands of hyalinized collagen; the tumor had biphasic histological appearance. Much of the cellular growth consisted of fusiform and polygonal cells with nuclei with granulated chromatin. Tumoral cells were disposed in fasciculi, with some cystic spaces (occasional with hematic content) and meningioma-like structures (component of type A thymoma). Alongside these, another component was present, consisting of small lymphocytes, regular and with condensed chromatin (thymocytes) and rare polygonal epithelial cells (component of type B thymoma) (Figure 4). The tumor was covered by a conjunctive capsule. Lymph nodes were 13 mm in size and reactive, with areas of lipomatous degeneration. In conclusion, the tumor was a type AB thymoma. Using the histological findings, as well as the intraoperative data, our final diagnosis was of a type AB thymoma, stage I Masaoka-Koga, encapsulated tumor with no microscopic invasion of nearby structures.

Discussion

Very large, giant thymic tumors are rare cases. Thymomas are tumors with slow growth, well tolerated by the patient. Advanced cases with secondary pleural or pericardial lesions are sometimes found (9). In 15-30% of cases, thymomas are discovered by accident, while symptoms of mediastinal suffering are only present in 10% of cases. Alongside clinical

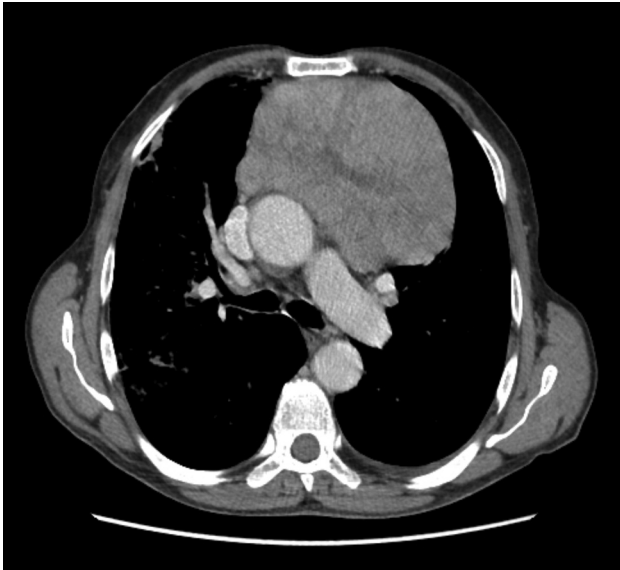


Figure 1. Mediastinal window of contrast computed tomography. The image reveals the presence of an encapsulated tumor of 139/123/105 mm with well-defined margins, developed in the antero-superior mediastinum.

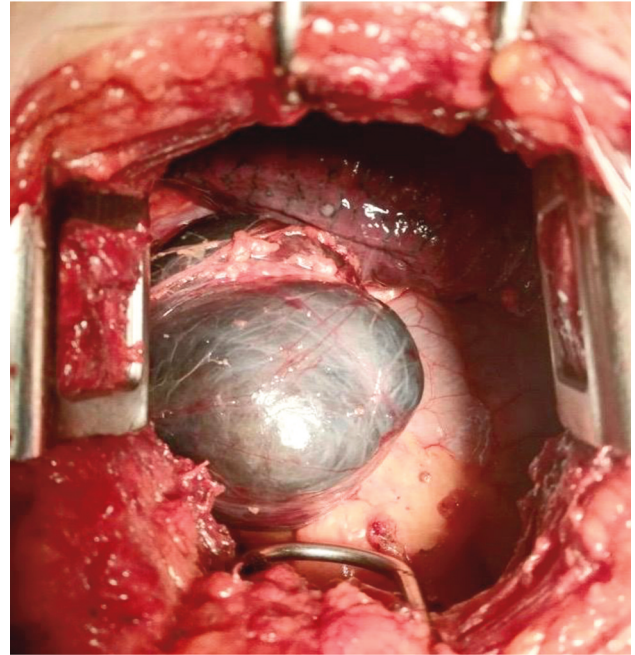


Figure 2. Intraoperative view of the thymoma.

symptoms, such as persistent cough, dyspnea and chest pain, other clinical signs may present due to the compression of mediastinal organs including the superior vena cava, venous brachiocephalic trunk, esophagus, phrenic and recurrent nerve. A case of type B3 thymoma with esophageal invasion was reported, with the tumor being visible during esophagoscopy; the first case reported so far (10).

Although superior vena cava syndrome is more frequently found in pulmonary cancer or lymphomas, it has also been described in thymomas (11). A case of thymoma with invasion of the right atrium and superior vena cava has been reported and successfully operated under cardio-pulmonary bypass (12). More so, 30% of thymomas have been found to invade the local mediastinal organs, pleura or pericardium (13). Superior vena cava syndrome in thymomas is very rare, found in only 4% of cases. The extrinsic compression of the superior vena cava or the brachiocephalic trunk is more common (14).

Some thymomas, such as the cystic ones can present with intracystic hemorrhage, having an effect of “acute” mediastinal compression (15). Others may present together with a hemorrhagic pericardial effusion, which may lead to cardiac tamponade (16). Ectopic localizations of thymomas have also been reported, in the left or right hemithorax or posterior to the left innominate vein (17-20). Giant thymomas with intrathoracic development (left or right) are often confused with solitary pleural fibromas (21). Particular cases of thymoma have also been described, such as an ectopic hamartomatous thymoma, with genetic testing revealing it to

be a neoplastic disease with changes in the histidyl-transfer ribonucleic acid (tRNA) ligase (*HARS*) gene (21, 22). Thymic tumors in general express programmed death-ligand 1 (PD-L1) of thymic epithelial origin and lymphocyte infiltrates. Observations have been made regarding an increased anti-tumoral activity inhibiting PD-L1 and a predisposition in developing paraneoplastic autoimmunity in patients with thymoma, especially in relapses (22).

Thymomas tend to have local recurrences and are associated with a series of autoimmune diseases such as autoimmune necrotising myopathy and severe multi-autoimmune syndrome (acute chronic inflammatory demyelinating polyneuropathy, Graves disease, leukocytoclastic vasculitis) (23). Pure white cell aplasia is a rare manifestation in type A+B2 mixed thymomas, associated with neutropenia and severe immunodeficiency (24). However, the most frequent autoimmune manifestation associated with thymoma is myasthenia gravis. It is present in almost 50% of patients with thymoma. Genetic studies revealed approximately 140 genes related to myasthenia gravis, pointing out that hypoxia-inducible factor 3 subunit alpha (*HIF3A*) is significantly increased in patients with myasthenia gravis. In this regard, it may play a role in the development of myasthenia gravis (25).

Some authors consider that the presence of a large intrathoracic tumoral mass associated with symptoms of myasthenia gravis should point towards a thymoma diagnosis (18). A series of histological and biological

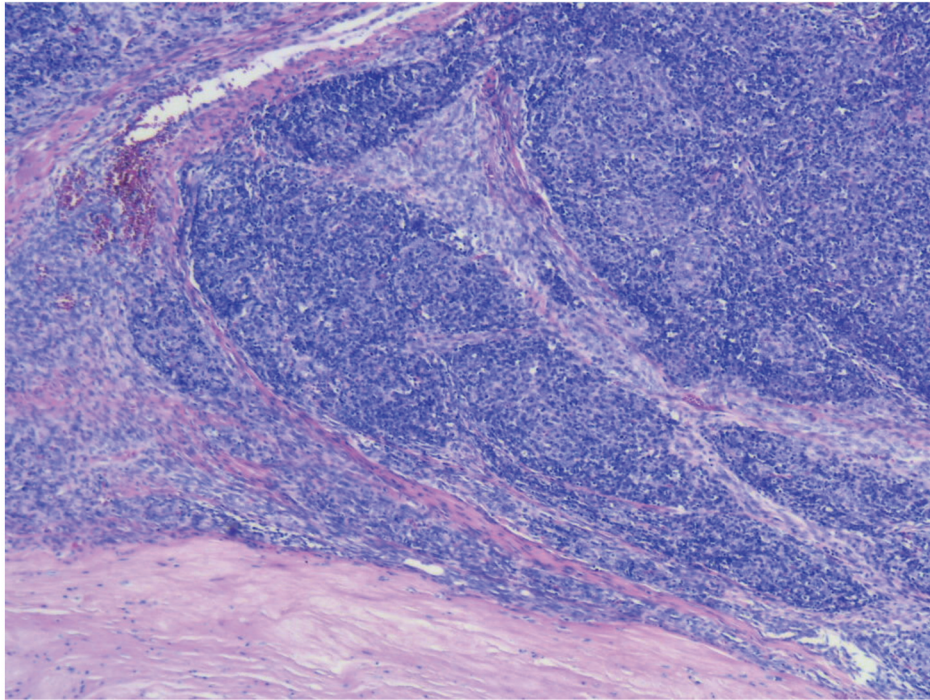


Figure 3. *Histopathological aspect of type AB thymoma. Hematoxylin–Eosin (HE) staining, ×40.*

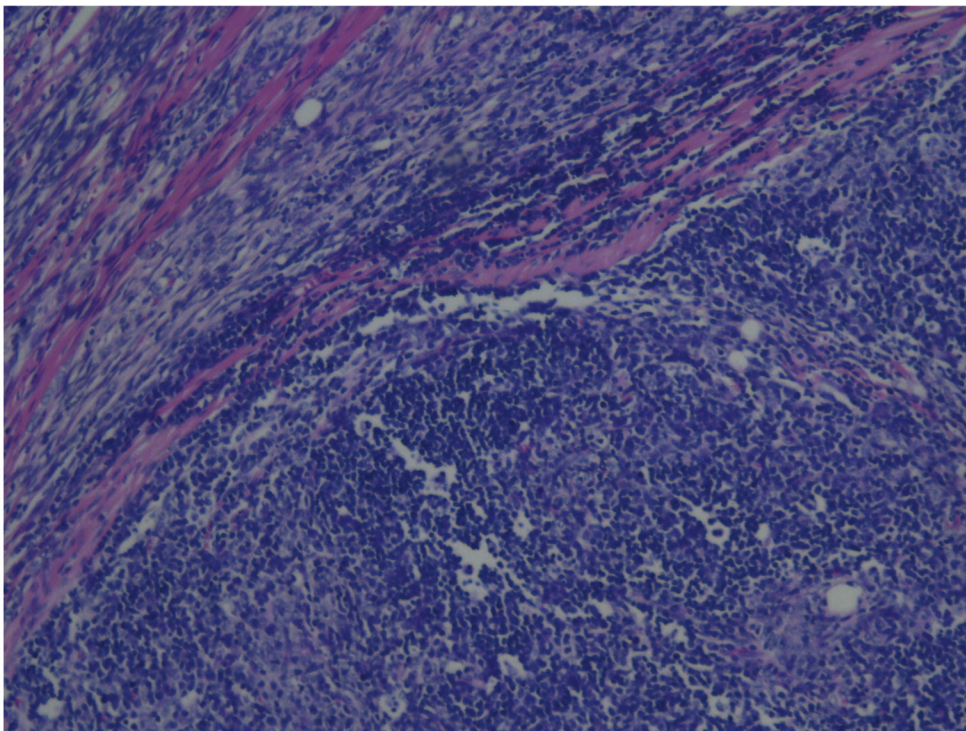


Figure 4. *Histopathological aspect of type AB thymoma. Hematoxylin–Eosin (HE) staining, ×200.*

parameters have been identified in patients with thymoma susceptible to developing myasthenia gravis: anti acetylcholine receptor antibodies, type B1 or B2 thymoma, presence of ectopic germinal thymic cells, local invasion by the thymoma, female sex with an age less than 50 (26).

Histopathologically, thymomas are made of different proportions of epithelial cells and lymphocytes. A characteristic of thymomas is that the histological types do not correlate with the clinical presentation, prognosis or survival. Regarding this, there have been cases described, such as a type A thymoma with vertebral metastases, diagnosed using positron emission tomography (PET) scans, having an increased reactivity to ^{18}F -Fluorodeoxyglucose (^{18}F -FDG) (27). Because of such cases, the Masaoka–Koga staging required modifications (28). Immunohistochemistry (IHC) is used for an accurate diagnosis of the thymoma type. This type of epithelial tumor is positive for cytokeratin, vimentin, epithelial membrane antigen and, in most cases, the presence of cells in string-of-pearls or streaming pattern.

For our patient we utilized IHC tests and found positive lymphocytes expressing cluster of differentiation (CD) 1a, terminal deoxynucleotidyl transferase (TdT) and CD5 and negative for CD34, cytokeratin (CK) and epithelial membrane antigen (EMA), leading to a diagnosis of type AB thymoma. Some authors noticed that in type A to B3 thymomas, a series of genetic mutations are more frequent, such as: *HARS*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) and *AKT1*. These genetic mutations help in differentiating thymomas from thymic carcinomas where the more frequent mutations are tumor protein 53 (TP53) and epidermal growth factor receptor (EGFR) (29).

Regarding imaging studies, a thoracic CT scan is the main investigation used in identifying thymomas. Studies have been realized which correlate CT findings, Masaoka–Koga staging and the *WHO* histological classification of thymomas. By doing this, a series of risk factors that do not depend on the disease evolution were identified using thoracic CT: infiltration of the mediastinal fat, pleural or pulmonary nodules, hemidiaphragm elevation as well as vascular invasion or pleural effusion. In the future, these factors will influence the management of this type of disease (30). Other authors suggested that in order to differentiate between low and high risk thymomas, an analysis of three-dimensional (3D) images from the CT scan should be performed, giving this method great reproducibility (31).

Recent studies have underlined that in the Masaoka–Koga classification, tumor size was not included as a criterium. However, there has been evidence showing a correlation between tumor size and rate of recurrence in complete thymic resections (32). Other authors consider that the size of the thymoma represents a significant prognostic factor: ≥ 5 cm points to a high risk of local recurrence and ≥ 8 cm

modifies disease-specific survival (33, 34). Similarly, other studies consider patients with tumors larger than 4 cm to have a worse prognosis than those with smaller tumors (34). This correlation was observed in patients with stage I thymoma (35). Risk factors for local recurrence of thymoma after surgery are: histological form according to the *WHO* classification, tumor size, Masaoka–Koga stage as well as the type of resection performed. Even so, complete aggressive resection, even in recurrence, remains the best course of treatment (36).

Surgical resection represents the gold standard in treatment of thymomas in both invasive and non-invasive cases (18). Giant encapsulated thymomas tend to have an expansive evolution, but without invading nearby organs or blood vessels. That is why surgical resection, independently of tumor size, must be taken into consideration (37). However, there are other authors that consider radiotherapy as an alternative to surgical treatment in recurrent thymoma. Using high doses of radiation with advanced techniques of precision and focus, results have been favorable, providing evidence towards the fact that recurrent thymomas are radiosensitive (38).

Median sternotomy is the gold standard regarding the surgical approach in favor of minimally invasive surgery used in thymomas. The completeness of resection is an important prognostic factor in the evolution of patients with thymoma (39). However, median sternotomy is not used much in large or giant tumors. It is used more frequently for cases with local extension of the tumor where complete excision is key for the therapeutic success.

Several studies comparing video-assisted thoracoscopic surgery (VATS) with classic surgery in thymoma treatment were performed and they concluded that the outcomes are similar, especially in cases associated with myasthenia gravis. VATS resection can be used for thymomas that only extend to the mediastinal pleura. For large encapsulated thymomas, with compression signs of the mediastinum, open surgery is preferred (40). Some authors compared the postoperative results of patients that underwent VATS and robotic surgery for the treatment of stages I and II thymomas and observed similar results, with both techniques having the same viability (41). In order to obtain proper access to both the mediastinum as well as the superior thoracic cavity, some authors prefer using a hemi-clamshell incision, especially for giant thymomas (42). For large thymomas developing towards either thoracic cavity, some surgeons prefer using a median sternotomy along with a splitting of the sternum along the intercostal space (19).

Giant encapsulated thymomas, with no local extension can be resected using an antero-lateral thoracotomy, preferred by most authors. In our case, the surgical resection was performed using a left antero-lateral thoracotomy through the fourth intercostal space, due to the tumor development being

mostly in the left hemithorax and no presence of mediastinal invasion on the CT scan. This type of approach has the advantage of being less invasive and much more versatile due to the ability to extend it. The surgical approach was safe, giving enough visibility in order to perform a complete resection of the tumor along with lymph node dissection.

Histological diagnosis along with IHC confirmed a stage I, type AB thymoma, in which case we considered complementary treatment not to be necessary. Patient follow up was done after one, three, six months and one year, with no signs of local recurrence (patient received surgical treatment 14 months ago). Even so, postoperative radiotherapy in thymomas is still a controversial theme. Although it does not increase relapse free survival or overall survival for stage II or III thymomas, it has a proven beneficial effect for stage II and III thymic carcinoids (43).

Some authors have suggested alternative treatments, such as CT-guided radiofrequency ablation for small stage I thymomas, observing the benefits of this method as it has a minimal rate of complications, removal is complete and costs are reduced (34). Although induction therapy is used especially in pulmonary neoplastic disease, it has also been used in thymic neoplastic disease (44). Comparative studies performed on patients that underwent surgery for thymic tumors with or without induction chemotherapy concluded that it may improve resectability, influencing the result in stage III and IV thymomas (45).

On the other hand, for invasive thymomas or unresectable stage IV thymic carcinoma an association between Tegafur, Gimeracil and Oteracil is recommended. Results obtained are similar to immunotherapy, but with much lower costs (46). Studies following the role of surgery depending on the stage of the disease show a smaller survival rate for patients with type B3 compared to those with types A, B1 or B2 thymomas. Long-term survival was increased in patients that also underwent surgical treatment for recurrences (47).

Local tumor extension remains the most important prognostic factor. In stage I, surgical treatment alone is recommended as treatment whereas, in stages II and III, adjuvant radiotherapy should be performed. Although each histological type is associated with different rates of recurrence and survival, a multicentre analysis revealed that age, stage as well as resectability are the main prognostic factors. The histological type is important in appreciating the chances of recurrence but not for survival (48, 49).

Conclusion

So far, in the literature, there is no consensus regarding the surgical approach of giant thymomas. Complete resection can be performed for large stage I and II thymomas using an antero-lateral thoracotomy. This type of approach has the advantage of being less invasive and much more versatile

due to the ability to extend it. Surgical treatment is still the main therapeutic method used for thymomas, no matter their size, local extension or recurrence.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

CS, AM, AG, IG, AZ performed the surgical procedure; VAT, NB, IB reviewed literature data; CD, FG performed preoperative investigation of the patient; CD, FG, FF performed perioperative and postoperative follow up of the patient; IB, FG FF, DR prepared the draft of the manuscript; IC was the advisor of the surgical procedures; CS, NB reviewed the final version of the manuscript. All Authors read and approved the final version of the manuscript.

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