Chapter 12
Epithelial Thymic Neoplasms

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Abstract The thymic epithelial tumors represent a heterogeneous group of thoracic cancers that originate in the thymus and are in the anterior mediastinum (de Jong WK, Blaauwgeers JL, Schaapveld M et al. Eur J Cancer 44:123–130, 2008). They are classified according to the World Health Organization (WHO) in Thymoma and Thymic Carcinoma (Marx A, Chan JK, Coindre JM et al. J Thorac Oncol 10:1383–1395, 2015). Thymomas may spread locally, but thymic carcinomas are much more aggressive (Proceedings of the First International Conference on Thymic Malignancies. August 20–21, 2009. Bethesda, Maryland, USA. J Thorac Oncol 2010;5:S259–S370, 2009).

Keywords Oncology · Chemotherapy · Thoracic oncology

12.1 Introduction

The thymic epithelial tumors represent a heterogeneous group of thoracic cancers that originate in the thymus and are in the anterior mediastinum [1]. They are classified according to the World Health Organization (WHO) in Thymoma and Thymic

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Carcinoma [2]. Thymomas may spread locally, but thymic carcinomas are much more aggressive. [3]

It is important to differentiate between thymic cancer and other conditions such as lung metastases, lymphoma (25% of cases), goiter and germ cell tumor (20% of cases) [1, 4]. About 50% of primary cancers in the anterior mediastinum are thymomas [5].

12.2 Incidence and Epidemiology

The thymic epithelial tumors present an annual incidence varying from 1.3 to 3.2 per million, with a 5-year survival rate for thymoma and thymic carcinoma of 90% and 55%, respectively [1, 6, 7]. Most patients with thymic neoplasm are between 40 and 60 years of age, with a similar incidence between sexes [8].

Thymomas predominate in adults (rare in children) whereas thymic carcinomas can be found in adolescents [9, 10]. The predominant histologies in thymic carcinoma are squamous cell carcinoma and undifferentiated carcinoma, therefore, they must always be differentiated from metastatic lung carcinoma [11].

There is no known risk factor or etiology, but the relation between thymoma and paraneoplastic syndromes such as myasthenia gravis (MG) is well established. Thymic carcinoma does not have the same relation and it is still unclear whether they both share a cell of common origin [12].

12.3 Clinical Manifestation and Diagnosis

12.3.1 Clinical Manifestations

Some patients are asymptomatic. Clinical presentation in thymomas and thymic carcinomas can be related to the size of the tumor and its effect on adjacent organs, such as cough, dyspnea, chest pain and superior vena cava syndrome. In thymic carcinomas, a more aggressive disease, they may present with lymph node involvement and extrathoracic metastases at diagnosis, as well as pleural and pericardial effusion [7, 13].

Paraneoplastic syndromes are common in thymomas and they can anticipate presentation, occur simultaneously or after treatment (with or without evidence of tumor recurrence). Up to one third of patients presents with autoimmune disorders, most frequently with myasthenia gravis (MG) in up to 30–50% of cases, mainly in types AB, B1 and B2, and frequently associated with anti-acetylcholine antibody. Suggestive symptoms are asthenia, dyspnea, hoarseness, diplopia and ptosis [14–16]. Other immune manifestations include pure red cell aplasia (5%) and hypogammaglobulinemia (Good's Syndrome: 5%). Thymectomy may lead to remission of

MG and pure red cell aplasia [17]. In thymic carcinoma, paraneoplastic syndromes are infrequent [18].

If a thymic epithelial tumor is suspected, a complete physical examination, including neurological examination, should be performed. Immunological evaluation, including blood count, reticulocytes, protein electrophoresis, as well as anti-acetylcholine antibodies and anti-nuclear antibodies should be requested. The presence of autoimmune disorders can affect the course of the disease, interfering with surgery, chemotherapy and radiotherapy [19].

12.3.2 Diagnosis

The standard imaging for the diagnosis of thymic tumors is computed tomography (CT) of the chest with contrast, it allows us to evaluate the mediastinum and pleura [19]. The need for pre-treatment biopsy depends on the resectability of the tumor, when required, the standard is CT- or ultrasound-guided percutaneous needle biopsy. [20–22].

The presence of mass localized in the anterior mediastinum associated with some of the autoimmune diseases mentioned above, closes the presumptive diagnosis of thymoma. Serum levels of lactate dehydrogenase (DHL), β-human chorionic gonadotropin (B-HCG), alphafetoprotein and thyroid hormone should be measured for differential diagnosis with lymphoma, germ cell tumors and goiter [19, 23].

The 18-Fluorodeoxyglucose positron emission tomography scan (PET-CT) is generally not recommended for the evaluation of thymic masses, and may be more useful in thymic carcinomas [24].

12.4 Anatomy and Pathology

The thymus is a lymphatic organ that acts on the maturation of the T lymphocytes. It is an irregular and lobed organ at maturity, slowly involutes in the adult phase, being replaced by adipose tissue. Ectopic thymic tissue can be found throughout the mediastinum and neck, and may be the explanation for thymomas outside the anterior mediastinum [12, 25].

The differentiation between thymoma and lymphoma in small biopsies can be difficult. The WHO classification was designed for surgical resection specimens; however, it may be used in small biopsies, anticipating possible discrepancies between them due to tumor heterogeneity and low sampling [26]. When presenting more than one histological pattern all should be listed and quantified, a component of thymic carcinoma should be listed first when present [19].

The WHO classification system for thymic neoplasms is the most widely used (Table 12.1) [27]. Suster and Moran [28] proposed a simpler classification that divides thymic tumors into 3 categories: Well differentiated (Types A, AB, B1 and B2), moderately differentiated (Type B3) and poorly differentiated (Type C).

Table 12.1 WHO Histologic Classification [27]

Type	Description
A	A tumor composed of a population of neoplastic thymic epithelial cells having spindle/ ovaI shape, lacking nuclear atypia, and accompanied by few or no nonneoplastic lymphocytes.
AB	A tumor in which foci having the features of type A thymoma are admixed with foci rich in lymphocytes.
B1	A tumor that resembles the normal functional thymus in that it combines large expanses having an appearance practically indistinguishable from normal thymic cortex with areas resembling thymic medulla.
B2	A tumor in which the neoplastic epithelial component appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a heavy population of lymphocytes. Perivascular spaces are common and sometimes very prominent. A perivascular arrangement of tumor cells resulting in a palisading effect may be seen.
B3	A type of thymoma predominantly composed of epithelial cells having a round or polygonal shape and exhibiting no or mild atypia. They are admixed with a mild component of lymphocytes, resulting in a sheetlike growth of the neoplastic epithelial cells.
C	A thymic tumor (thymic carcinoma) exhibiting clear-cut cytologic atypia and a set of cytoarchitectural features no longer specific to the thymus, but rather analogous to those seen in carcinomas of other organs. Type C thymomas lack immature lymphocytes; whatever lymphocytes may be present are mature and usually admixed with plasma cells.

Thymic carcinomas are histologically classified as low or high grade. Low-grade carcinomas include squamous cell carcinomas, mucoepidermoid, and basaloid, generally have a more favorable presentation with a median survival of 25.4 months. High-grade carcinomas include lymphoepitheliomalike, undifferentiated, sarcomatoid, and clear cell carcinomas, which present a worse prognosis with a median survival of 11.3 months [13, 29].

Immunohistochemical markers may be useful, including cytokeratins, p63 expression and deoxynucleotidyl transferase in immature T cells (Absent in type A). In thymic carcinomas immunohistochemistry may presents anti CD117 (KIT) and anti CD5, positive in approximately 80% of carcinomas with thymic origin [30].

Overexpression of EGFR is found in more than two thirds of patients, mostly in subtypes B2 and B3. Overexpression of c-kit is common in thymic carcinomas although its mutation is less frequent. [31, 32]

12.5 Staging and Risk Assessment

The most used staging for thymic tumors is Masaoka-Koga (Table 12.2) and is related to overall survival. It is a system of surgical pathology that can only be evaluated after surgical resection [33, 34].

The Tumor-Node-Metastasis staging (TNM) for thymic malignancies was based on an international retrospective database with more than 10,000 cases (Table 12.3)

Table 12.2 Masaoka Staging System [33]

Stage	Description
I	Macroscopically completely encapsulated and microscopically no capsular invasion
IIA	Microscopic invasion into capsule
IIB	Macroscopic invasion into surrounding fatty tissue or mediastinal pleura
III	Macroscopic invasion into neighboring organ, i.e., pericardium, great vessels, or lung
IVA	Pleural or pericardial dissemination
IVB	Lymphogenous or hematogenous metastasis

Table 12.3 TNM Classification [35]

T-primary tumor			
T0	No evidence of primary tumor		
T1	Tumor encapsulated or extending into the mediastinal fat; may involve the mediastinal pleura		
A	Tumor with no mediastinal pleura involvement		
B	Tumor with direct invasion of mediastinal pleura		
T2	Tumor with direct invasion of the pericardium (either partial or full thickness)		
T3	Tumor with direct invasion into any of the following: lung, brachiocephalic vein, superior vena cava. phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins		
T4	Tumor with invasion into any of the following: aorta (ascending, arch, or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus		
N-regional lymph nodes			
N0	No regional lymph node metastasis		
N1	Metastasis in anterior (perithymic) lymph nodes		
N2	Metastasis in deep intrathoracic or cervical lymph nodes		
M - distant metastasis			
M0	No pleural, pericardial, or distant metastasis		
M1	Pleural, pericardial, or distant metastasis		
A	Separate pleural or pericardial nodule(s)		
B	Pulmonary intraparenchymal nodule or distant organ metastasis		
Stage grouping			
Stage	T	N	M
I	T1a,b	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	Any T	N1	M0
IVA	Any T	N0,1	M1a
IVB	Any T	N2	M0,M1a
IVB	Any T	Any N	M1b

and was incorporated into the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system. It has the advantage of being suitable for both thymoma and thymic carcinoma and may be useful in evaluating resectability because the level of T1-T3 invasion refers to structures susceptible to surgical resection while the level of T4 invasion includes non-resectable structures [35].

The main prognostic factor is the complete surgical resection surpassing the tumor stage and the histology [34, 36]. Most patients, up to 50–60% of cases depending on the stage, do not die of tumor progression [37]. One of the causes of death in patients with thymoma are autoimmune disorders, occurring in up to 25% of cases, especially in the early stages [19].

12.6 Surgical Treatment

Total thymectomy, including removal of the tumor, residual thymic gland and perithymic fat, is the procedure of choice for resectable thymic tumors in patients who can tolerate surgery, achieving high survival rates at 10 years for thymomas, depending on the integrity of the resection, as in stages I and II with rates of 90 and 70%, respectively [10, 34]. For tumors that invade other structures it is necessary to remove all these structures in block [38].

Removal of anterior mediastinal and anterior cervical lymph nodes is routinely recommended. Sampling of other intrathoracic lymph nodes is suggested in stages III/IV. For thymic carcinomas, systematic lymphadenectomy with a broad lymph node approach is strongly recommended because of the high rates of lymphatic dissemination compared to thymomas (20% × 3%) [39, 40].

For patients with tumor recurrence, surgical resection may result in prolonged survival for selected patients with localized disease [41].

12.7 Radiotherapy

Adjuvant radiotherapy is not recommended for fully resected Stage I thymomas and the lymph nodes should not be irradiated routinely because of the low risk of compromising them [33, 42, 43]. For stage II patients completely resected with capsular invasion or aggressive histology (B2/B3), adjuvant radiotherapy may be considered, whereas stage III, due to the high risk of local recurrence, is recommended with a prolongation in recurrence free survival and overall survival [42, 44, 45]. For patients with unresectable disease the dose of 60–70 Gy is recommended [46].

In adjuvant radiotherapy, the recommended dose is 45–50 Gy for patients with free margins, 54 Gy for patients with microscopically positive margins and 60 Gy or more for patients with macroscopic residual disease. Adjuvant radiotherapy should be started ideally within 3 months after surgery [46].

For thymic carcinomas the radiotherapy is recommended the similarity of the thymoma, considering the greater rate of recurrence of the same, being optional in stage I [9, 47].

12.8 Chemotherapy

12.8.1 Induction Chemotherapy

For the locally advanced thymic tumors, which were considered unresectable in the imaging studies, a biopsy should be performed followed by induction chemotherapy. The most studied regimen is CAP (Cisplatin 50 mg/m2, Doxorubicin 50 mg/m2 and Ciclophosphamide 500 mg/m2) every 3 weeks for about two to four cycles before reassessment with overall response rate of 69.6%. [48–50].

Chemoradiotherapy associated with Cisplatin and Etoposide can be performed for thymic carcinomas [51, 52].

12.8.2 Chemoradiotherapy

When surgery cannot be performed, either because of poor performance or due to technical difficulties, one option is to offer definitive radiation therapy after chemotherapy or to consider chemoradiotherapy with Cisplatin and Etoposide (60–66 Gy) [19, 50].

12.8.3 Adjuvant Chemotherapy

Adjuvant chemotherapy is not recommended for thymomas with complete resection or with microscopic surgical margins [36, 53].

In thymic carcinomas, adjuvant chemotherapy may be considered after incomplete resection, especially when induction chemotherapy has not been offered, due to the high rates of relapse [19].

12.8.4 Palliative Chemotherapy

For patients with unresectable/metastatic disease, systemic treatment should be considered to control the symptoms [20]. The most commonly used regimen for thymomas is CAP [54]. Other less aggressive options are Carbo-Px (Carboplatin AUC 5 plus Paclitaxel 200 mg/m^2) every 3 weeks or PE/VIP (Cisplatin and Etoposide – with or without Ifosfamide), also used as second line therapy [55–57]. As sequential therapies, we have options like Pemetrexed and the combination of

Gemcitabine plus Capecitabine [58, 59]. Re-exposure to a previous regimen should be considered when a good response was initially achieved associated with a long disease-free period [60].

In patients with thymoma and Octreoscan positive, not candidates for chemotherapy, Octreotide (associated or not with Prednisone) may be used [61].

Thymic Carcinoma does not respond well to chemotherapy. The highest response rate in clinical trials is with the Carbo-Px [55]. The ADOC regimen (Cisplatin 50 mg/m^2, Doxorubicin 40 mg/m^2, Vincristine 0.6 mg/m^2 and Cyclophosphamide 700 mg/m^2) is also effective, but it is more toxic than Carbo-Px [62]. Second-line chemotherapy has been poorly studied and is performed as in the thymoma.

12.9 Molecularly Targeted Therapy

The molecular characterization of thymic epithelial tumors has identified feasible targets for targeted therapy as molecular changes in KIT, vascular endothelial growth factor (VEGFRs) and mammalian target of rapamycin (mTOR) receptors [63].

Patients with thymic carcinoma may have overexpression of the KIT gene in up to 80% of cases; however, only 10% have the c-kit mutation and in these cases Sorafenib, Sunitinib or Imatinib may be useful as a therapeutic option for refractory tumors (Off-Label) [64, 65]. For patients without c-Kit mutation, Imatinib should not be used. Patients with thymoma do not have a c-kit mutation [66].

Sunitinib may be an off-label option for patients with thymic carcinoma without the c-Kit mutation based on a phase II study that showed response and disease control rate [64]. There is no evidence regarding the use of other anti-angiogenic drugs such as Bevacizumab [19].

Everolimus was also evaluated in a phase II study showing a response rate of 22%, therefore, it can be considered as an off-label option for refractory thymic tumors [67].

12.10 Follow-Up

Although there are no clinical trials that show benefit, monitoring with chest images is recommended [20, 33].

A chest CT scan should be ordered 3–4 months after surgery [19].

After treatment for resectable stage I/II thymomas, computed tomography of the chest should be performed annually within the first 5 years and every 2 years thereafter [19]. For stage III/IV thymomas or resected with compromised margins, computed tomography of the chest should be performed every 6 months for the first 2 years and annually thereafter [19, 20].

For resected thymic carcinoma, computed tomography of the chest is recommended every 6 months for the first 2 years and annually thereafter [19, 20].

Follow-up should be maintained for 10–15 years because of the risk of late recurrence, especially in thymomas [68].

Patients with thymoma are at increased risk of developing a second neoplasm such as non-Hodgkin's lymphoma, gastrointestinal cancer, and soft tissue sarcoma [69].

Questions

1. M. S., 32 years old, female, performed Chest Radiography, which showed mediastinal enlargement, due to cough. During the investigation, he performed a thorax CT that showed mass in the anterior mediastinum without invasion of adjacent structures. She has no history of smoking or other comorbidities.
   Which the initial conduct?

   A. Biopsy
   B. Follow-up
   C. PET-CT
   D. **Surgery**

J: Total thymectomy, including removal of the tumor, residual thymic gland and perithymic fat, is the procedure of choice for resectable thymic tumors in patients who can tolerate surgery, achieving high survival rates at 10 years for thymomas, depending on the integrity of the resection, as in stages I and II with rates of 90 and 70%, respectively.

2. Still on the above case, a thymectomy was performed whose anatomopathological showed a 4 cm encapsulated thymoma without capsular invasion, type A (WHO classification).

   What is the stage of this thymoma?

   A. **Masaoka I**
   B. Masaoka II
   C. Masaoka III
   D. Masaoka IV

J: The most used staging for thymic tumors is Masaoka-Koga and is related to overall survival. It is a system of surgical pathology that can only be evaluated after surgical resection.

The Masaoka staging:

Stage	Description
I	Macroscopically completely encapsulated and microscopically no capsular invasion
IIA	Microscopic invasion into capsule
IIB	Macroscopic invasion into surrounding fatty tissue or mediastinal pleura
III	Macroscopic invasion into neighboring organ, i.e., pericardium, great vessels, or lung
IVA	Pleural or pericardial dissemination
IVB	Lymphogenous or hematogenous metastasis

3. According to the surgical staging above, what would be the most appropriate therapy?

   A. **Clinical Surveillance**
   B. Adjuvant radiotherapy
   C. Adjuvant chemotherapy
   D. Radiation therapy followed by chemotherapy

J: Adjuvant radiotherapy is not recommended for fully resected Stage I thymomas and the lymph nodes should not be irradiated routinely because of the low risk of compromising them. Adjuvant chemotherapy is not recommended for thymomas with complete resection or with microscopic surgical margins.

4. F. S., 52 years old, male, was admitted to the emergency room due to intense asthenia, palpebral ptosis and diplopia. Laboratory tests were performed to show the presence of the anti-acetylcholine antibody. An anterior mediastinal mass was visualized on chest CT.

   What is the probable diagnosis?

   A. Germ cell tumor
   B. **Thymoma**
   C. Thymic Carcinoma
   D. Goiter

J: The presence of mass localized in the anterior mediastinum associated with some of the autoimmune diseases mentioned above, closes the presumptive diagnosis of thymoma. Up to one third of patients presents with autoimmune disorders, most frequently with myasthenia gravis (MG) in up to 30–50% of cases, mainly in types AB, B1 and B2, and frequently associated with anti-acetylcholine antibody.

5. What treatment could bring remission of the paraneoplastic syndrome mentioned above?

   A. Chemotherapy
   B. Radiotherapy
   C. **Thymectomy**
   D. Clinical treatment only

J: Paraneoplastic syndromes are common in thymomas and they can anticipate presentation, occur simultaneously or after treatment (with or without evidence of tumor recurrence). Up to one third of patients presents with autoimmune disorders, most frequently with myasthenia gravis (MG) in up to 30–50% of cases. Other immune manifestations include pure red cell aplasia (5%) and hypogammaglobulinemia (Good's Syndrome: 5%). Thymectomy may lead to remission of MG and pure red cell aplasia.

6. Which tests should be performed in the differential diagnosis of mediastinal mass?

   A. lactate dehydrogenase
   B. β-human chorionic gonadotropin and alphafetoprotein
   C. thyroid hormone
   D. **All above**

J: Serum levels of lactate dehydrogenase (DHL), β-human chorionic gonadotropin (B-HCG), alphafetoprotein and thyroid hormone should be measured for differential diagnosis with lymphoma, germ cell tumors and goiter.

7. What are the main paraneoplastic syndromes associated with thymoma?

   A. Myasthenia gravis
   B. Pure red cell aplasia
   C. Good's Syndrome
   D. **All above**

J: Up to one third of patients presents with autoimmune disorders, most frequently with myasthenia gravis (MG) in up to 30–50% of cases. Other immune manifestations include pure red cell aplasia (5%) and hypogammaglobulinemia (Good's Syndrome: 5%).

8. L. L, 44 years old, female, underwent thymectomy, whose pathological anatomy revealed thymic carcinoma with macroscopic invasion of neighboring structures and incomplete resection.

   What's the next conduct?

   A. Clinical Surveillance
   B. Radiotherapy with 54 Gy
   C. **Radiotherapy with 60 Gy**
   D. Chemotherapy

J: Adjuvant radiotherapy is recommended for stage II patients completely resected with capsular invasion or aggressive histology (B2/B3), whereas stage III, due to the high risk of local recurrence, is recommended with a prolongation in recorrence free survival and overall survival. In adjuvant radiotherapy, the recommended dose is 45–50 Gy for patients with free margins, 54 Gy for patients with microscopically positive margins and 60 Gy or more for patients with macroscopic residual disease. Adjuvant radiotherapy should be started ideally within 3 months after surgery.

9. Which histology of thymic carcinoma is associated with an unfavorable outcome?

   A. Squamous cell carcinoma
   B. **Clear Cell Carcinoma**
   C. Mucoepidermoid Carcinoma
   D. Basaloid Carcinoma

J: Thymic carcinomas are histologically classified as low or high grade. Low-grade carcinomas include squamous cell carcinomas, mucoepidermoid, and basaloid,

generally have a more favorable presentation with a median survival of 25.4 months. High-grade carcinomas include lymphoepitheliomalike, small, undifferentiated, sarcomatoid, and clear cell carcinomas, which present a worse prognosis with a median survival of 11.3 months.

10. What is the main prognostic factor in thymic epithelial tumors?

    A. **Complete resection**
    B. Age
    C. Sex
    D. Presence of paraneoplastic syndrome

J: Total thymectomy, including removal of the tumor, residual thymic gland and perithymic fat, is the procedure of choice for resectable thymic tumors in patients who can tolerate surgery, achieving high survival rates at 10 years for thymomas, depending on the integrity of the resection, as in stages I and II with rates of 90 and 70%, respectively. For tumors that invade other structures it is necessary to remove all these structures in block.

11. Paraneoplastic syndromes manifest in what period of the disease?

    A. Before diagnosis
    B. During illness
    C. After treatment
    D. **All above**

J: Paraneoplastic syndromes are common in thymomas and they can anticipate presentation, occur simultaneously or after treatment (with or without evidence of tumor recurrence).

12. For locally advanced thymic tumors what is the best therapeutic option?

    A. Surgery
    B. Radiation Therapy + Chemotherapy
    C. **Induction chemotherapy**
    D. Palliative chemotherapy

J: For the locally advanced thymic tumors, which were considered unresectable in the imaging studies, a biopsy should be performed followed by induction chemotherapy. The objective of induction chemotherapy is to achieve complete tumor resection, which improves overall survival.

13. What is the most studied chemotherapy regimen for locally advanced thymoma?

    A. **CAP**
    B. Carboplatin Plus Paclitaxel
    C. Cisplatin plus Etoposide
    D. Ifosfamide

J: The most studied regimen is CAP (Cisplatin 50 mg/m2, Doxorubicin 50 mg/m2 and Ciclophosphamide 500 mg/m2) every 3 weeks for about two to four cycles before reassessment with overall response rate of 69.6%.

14. What is the first choice in the palliative treatment of thymic carcinoma?

    A. CAP
    B. **Carboplatin Plus Paclitaxel**
    C. Cisplatin plus Etoposide
    D. Ifosfamide

J: Thymic Carcinoma does not respond well to chemotherapy. The highest response rate in clinical trials is with the Carboplatin AUC5 plus Paclitaxel 200 mg/m^2 every 3 weeks with objective response rate of 21,7%. Progression-free survival (PFS) was 5 months and Median survival time was 20.0 months.

15. Which of the following schemes can be used as a second line?

    A. CAP
    B. Carboplatin Plus Paclitaxel
    C. Gemcitabine plus Capecitabine
    D. **All above**

J: The most commonly used regimen for thymomas is CAP. Other less aggressive options are Carbo-Px (Carboplatin AUC 5 plus Paclitaxel 200 mg/m2) every 3 weeks or PE/VIP (Cisplatin and Etoposide – with or without Ifosfamide), also used as second line therapy. As sequential therapies, we have options like Pemetrexed and the combination of Gemcitabine plus Capecitabine. Re-exposure to a previous regimen should be considered when a good response was initially achieved associated with a long disease-free period

Clinical Case

M.C.T., 40 years old, born in Pernambuco, begins follow-up with clinical neurology in 2010 complaining of intense asthenia associated with diplopia. During the investigation carried out research of antibodies with positivity of the anti-acetylcholine antibody.

With the diagnosis of myasthenia gravis, a chest CT scan (Fig. 12.1) revealed a mass of finely heterogeneous attenuation in the thymus topography, measuring 3.0 × 1.5 cm, which may correspond to thymic neoplasia.

She was no history of comorbidities. It was opted for thymectomy with the diagnosis of Thymoma B3 by WHO classification and Masaoka I staging.

During follow-up with neurology she presented some exacerbations of myasthenia gravis, the last one being in 2015, maintaining the use of Pyridostigmine and Prednisone.

In 2015, it was visualized in chest CT two pleural nodules, one in right apex measuring 7.0 × 5.1 cm and other pleurodiaphragmatic measuring 3.7 × 1.3 cm. Biopsy confirmed recurrence of Thymoma B3.

It was discussed case with the Thoracic Surgery and they opted for induction chemotherapy with CAP. After the first cycle patient presented respiratory symptoms associated with neutropenia grade 4 and needed hospitalization for administration of antibiotics. After the third cycle, although with the administration of granulocyte colony stimulating factor, the patient is admitted to an intensive care unit due to pneumonia and grade 4 neutropenia/thrombocytopenia, requiring orotracheal intubation.

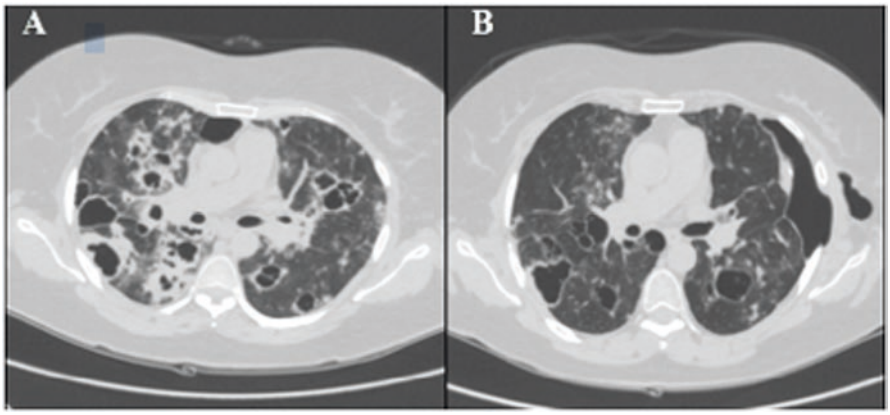

Fig. 12.1 (**a**) Chest CT performed on 07/2017 showing bilateral cavitary lesions with soft tissue density content. (**b**) Chest CT performed on 09/2017, after antibiotic therapy and immunoglobulin infusion, showing reduction of cavitations. (Source: Provided by the Department of Clinical and Experimental Oncology of UNIFESP)

It was performed chest CT after the fourth cycle with partial response of the lesions, measuring 3.5 × 3.1 cm located at the apex of the lung and 1.6 × 0.8 cm at pleurodiaphragmatic.

After 40 days of the end of chemotherapy, the patient performs thoracotomy with complete resection of pleural lesions (Thymoma B3) and mediastinal fat (Absence of neoplasia)

The patient remained in follow-up for 2 years, during which time she had several upper respiratory infections, pulmonary tuberculosis and hospitalization due to widespread herpes zoster.

In 2017 presented pulmonary infection with a need for hospital admission, on CT of thorax visualized bilateral excavated nodules and ground glass opacities associated with right hilar lymph node measuring 1.3 cm. Biopsy performed with diagnosis of pneumocystosis.

In laboratory tests and immunoglobulin dosages detected IgM <5.0 UI/ml, IgG <30.0 UI/ml and IgA 43 UI/ml. Lymphocytes: CD3 2046 células/mm^3; CD4 1006 células/mm^3; CD8 1246 células/mm^3; CD19 0 células/mm^3 and NK 111 células/mm^3. After confirmed the diagnosis of Good's Syndrome was initiated follow-up with immunology and realized monthly Immunoglobulin infusions.

After the fourth application and beginning of especific treatment, there was clinical and laboratory improvement. In the last staging, the patient was no evidence of disease, with improvement of the cavitated lesions.

This case illustrates the potential of the thymoma to manifest paraneoplastic syndromes. Up to one third of patients can present with autoimmune disorders, most frequently myasthenia gravis (MG) in up to 30–50% of cases. The hypogammaglobulinemia (Good's Syndrome) can be present in up to 5% of cases. (Fig. 12.1).

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