ARROCase: Thymoma

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Clinical Presentation

• 58 year-old woman presents to an ophthalmologist with ptosis, diplopia, malaise, and muscle weakness with chewing.
  – **PMH/PSH**: None.
  – **FH**: No family history of malignancy or neuromuscular disease.
  – **SH**: Married, works as insurance agent. Never smoker, no alcohol/drug use.
  – **Medications/allergies**: Non-contributory.
  – **Physical Examination**: +Diplopia, bilateral ptosis. Mild proximal muscle weakness.
  – Suspecting myasthenia gravis, she is referred to a neurologist.
Workup

• Neurology consultation
  – AChR modulating, blocking, and binding antibodies were each elevated.
  – A clinical diagnosis of myasthenia gravis was made, and she was started on prednisone and pyridostigmine with symptomatic improvement.
  – Prednisone was later tapered and mycophenolate was started.

• Imaging was ordered to rule out thymoma
  – **Chest x-ray** demonstrated a left anterior mediastinal mass.
  – **Chest CT+C** demonstrated an anterior mediastinal mass measuring 6.6x5.3x2.4cm without gross invasion of the lung or heart and without nodal, pleural, or intrathoracic metastases.
Workup

- **Chest X-Ray** demonstrated a left-sided mass obscuring the aortic contour in the anterior mediastinum.
Workup

- **Chest CT** demonstrated a left-sided anterior mediastinal mass measuring 6.6x5.3x2.4cm without gross invasion of the lung, pleura, or heart, and without nodal, pleural, or intrathoracic metastases.
Workup

- **Further workup:**
  - **CBC/CMP** unremarkable
  - **Pulmonary function testing** demonstrated FVC 3.56L (85% predicted), FEV1 2.68 (81% predicted), suggesting possible restrictive process.
  - **AFP, beta-HCG** were not elevated.

- **Consultation with thoracic surgery:**
  - Myasthenic symptoms had resolved with pyridostigmine/prednisone.
  - The anterior mediastinal tumor was clinically consistent with a resectable thymoma, and initial biopsy was not indicated.
  - Recommendation was for a median sternotomy and total thymectomy.

- **Differential diagnosis (anterior mediastinal mass)**
  - Thymoma, thymic carcinoma, thymic cyst, carcinoid, thymic lipoma, seminoma, germ cell tumor, teratoma, lymphoma, enlarged/ectopic thyroid
Resection

- **Resection:**
  - After median sternotomy, the mass encased the left phrenic nerve and was adherent to the left upper lobe and anterolateral (left) pericardium
  - Total thymectomy, *en bloc* resection of the left phrenic nerve, partial pericardiectomy, and *en bloc* left upper lobe wedge resection were performed for gross total resection.
  - Uncomplicated postoperative course

- **Surgical Pathology:**
  - **Histology:** thymoma, WHO Type B2, 5.5cm. Lymphocytes admixed with lesional cells. [1]
  - **Extent:** transcapsular invasion with involvement of the visceral pleura, parietal pleura, and pericardium
  - **Margins:** microscopic positive posterior margin (R1), 0.1cm to right+left lateral margins
  - **Modified Masaoka stage:** stage IIIA (+pericardial/pleural invasion, no great vessel invasion) [2]
  - **AJCC 8th edition stage:** pT2 cN0M0 (II)

- **Post-discharge follow-up:** no dyspnea despite left phrenic nerve sacrifice.
Adjuvant Therapy

- **Radiotherapy: [2,3]**
  - Given extent (Masaoka stage II A) and microscopic positive margin, adjuvant radiotherapy was recommended.
  - **Simulation:**
    - Supine, arms over head, vac bag, IV contrast
    - 4DCT, inspiration breath hold, expiration breath hold CT with 2mm slice thickness
  - **Technique:** volumetric-modulated arc radiotherapy
Adjuvant Therapy

• Radiotherapy: [2,3]
  – Target volumes:
    • Fuse pre-resection imaging and contour pre-resection GTV
    • Postoperative CTV encompasses entire surgical bed, clips, anterior mediastinum, and areas of pericardial/pleural contact with the preoperative GTV at risk for microscopic disease. Discussion with surgeon encouraged.
    • Motion-inclusive ITV vs. inspiration breath hold
    • Elective nodal irradiation not indicated
    • CTV-to-PTV margin dictated by image-guidance and LINAC tolerance (5mm)
  – Prescription dose:
    • 54 Gy in 30 fractions prescribed to cover 95% of PTV
    • Motion management/IGRT: daily CBCT with respiratory gating during treatment to exclude extreme breaths vs. inspiration breath hold
• Chemotherapy: not indicated
Postoperative Radiotherapy: CTV
Postoperative Radiotherapy: CTV
Postoperative Radiotherapy: CTV
Postoperative Radiotherapy: Plan

100% IDL – 54 Gy
75% IDL – 40.5 Gy
50% IDL – 27 Gy
20% IDL – 10.8 Gy
Postoperative Radiotherapy: Plan

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PTV
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PTV
CTV

100% IDL – 54 Gy
75% IDL – 40.5 Gy
50% IDL – 27 Gy
20% IDL – 10.8 Gy
Postoperative Radiotherapy: Plan

- **VMAT plan:**
  - **Fields:** Two arcs, 6 MeV, 54 Gy in 30 fractions prescribed to 95% PTV coverage
  - **Lungs:** Mean 9.7 Gy; V30=6%; V20=12%; V5=61%
  - **Heart:** Mean 8.9 Gy; V30=9%; V10=25%
  - **Esophagus:** Dmax 32 Gy; mean 12 Gy
  - **Great vessels:** D0.03cc <=108%
  - **Proximal tracheobronchial tree:** D0.03cc <=108%
  - **Full list of proposed constraints:** Gomez et al. [3]
Radiotherapy Course and Follow-Up

- She experienced grade 1 fatigue during radiotherapy, with no dyspnea, esophagitis, or weight loss.
- A surveillance chest CT with contrast was completed six months after radiotherapy per NCCN guidelines, with no evidence of intrathoracic recurrence.
  - Recurrence patterns defined in Gomez et al. [3]
- NCCN guidelines for follow-up: [2]
  - Chest CT with contrast every 6 months for the first two years, then annually for 5 years (thymic carcinoma) or 10 years (thymoma)
Thymic Masses: Presentation

- **Symptoms:**
  - **Myasthenic symptoms:** ptosis, diplopia, dysphagia, difficulty chewing, dysarthria, hypophonia, facial weakness, dyspnea. 30-50% of patients with thymomas have myasthenic symptoms. 10-20% of patients with myasthenia gravis have a thymoma.
  - **Mass effect:** dyspnea, chest pain, cough, odynophagia, SVC syndrome, pleural/pericardial effusions, restrictive lung physiology
  - **Phrenic nerve involvement:** dyspnea, diaphragmatic paralysis
  - **Other paraneoplastic syndromes:** variety of other common and uncommon autoimmune diseases have been associated with thymomas, including pure red cell aplasia, immunodeficiencies, and thymoma-associated multiorgan autoimmunity.
    - **Management:** short- and long-term immunosuppression, thymectomy, pyridostigmine/IVIG (MG), supportive transfusions (PRCA). Thymectomy alone may not reverse these syndromes.

- **Epidemiology:** [2]
  - Incidence: 1.5 cases per million, similar incidence between men and women
  - Most common adult primary thymic neoplasm
  - Highest incidence between 40-60 years of age
Thymic Masses: Work-Up

- **NCCN 1.2020 recommended work-up:** [2]
  - **Required:** Chest CT with contrast, beta-HCG+AFP (rule out germ cell tumors), CBC/CMP, AChR antibodies
  - **Optional:** PFTs, PET/CT, MRI (for equivocal CT, may help distinguish thymoma vs. thymic carcinoma vs. thymic cyst vs. other histologies)
  - **Biopsy:**
    - **Upfront resection without biopsy** can be pursued if a primary thymic neoplasm is felt to be likely (well-defined anterior mediastinal mass, negative beta-HCG/ AFP, absence of adenopathy, absence of continuity with thyroid).
    - For **unresectable** tumors or if there is **uncertainty** regarding histology, core biopsy should be performed (CT-guided, open, or thoracoscopic). Thoracentesis and cytology can also be pursued to establish diagnosis.
# Thymic Neoplasms: Classification

<table>
<thead>
<tr>
<th>WHO Type</th>
<th>Muller-Hermelink</th>
<th>Levine and Rosai</th>
<th>Distribution</th>
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<tbody>
<tr>
<td>Type A</td>
<td>Medullary type thymoma</td>
<td>Encapsulated</td>
<td>4-7% (17% MG*)</td>
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<tr>
<td>Type AB</td>
<td>Mixed type thymoma</td>
<td>Encapsulated</td>
<td>28-34% (16% MG)</td>
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<tr>
<td>Type B1</td>
<td>Predominantly cortical</td>
<td>Malignant type I</td>
<td>9-20% (57% MG)</td>
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<tr>
<td>Type B2</td>
<td>Cortical type</td>
<td>Malignant type I</td>
<td>20-36% (71% MG)</td>
</tr>
<tr>
<td>Type B3</td>
<td>Well-differentiated carcinoma</td>
<td>Malignant type I</td>
<td>10-14% (46% MG)</td>
</tr>
<tr>
<td>Type C (thymic</td>
<td>Thymic carcinoma</td>
<td>Malignant type II</td>
<td>5-10% (&lt;10% MG)</td>
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<tr>
<td>carcinoma)</td>
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*Incidence of Myasthenia Gravis by WHO Type.
# Thymic Neoplasms: Staging

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<tbody>
<tr>
<td>I</td>
<td>96%</td>
</tr>
<tr>
<td>II A</td>
<td>86%</td>
</tr>
<tr>
<td>II B</td>
<td>86%</td>
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<td>III A</td>
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<td>III B</td>
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<td>IV A</td>
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<tr>
<td>IV B</td>
<td>50%</td>
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</tbody>
</table>
# Thymic Neoplasms: Staging

| **T category** | **TX**: primary tumor cannot be assessed  
|               | **T0**: no evidence of primary tumor  
|               | **T1**: tumor encapsulated or extending into mediastinal fat  
|               | **T2**: direct invasion of the pericardium (partial or full-thickness)  
|               | **T3**: direct invasion into any of the following: lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins  
|               | **T4**: invasion into any of the following: aorta, arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus  |
| **N category** | **NX**: regional nodes cannot be assessed  
|               | **N0**: no regional nodal metastases  
|               | **N1**: metastasis in anterior (perithymic) lymph nodes  
|               | **N2**: metastasis in deep intrathoracic or cervical lymph nodes  |
| **M category** | **M0**: no pleural, pericardial, or distant metastases  
|               | **M1a**: separate pleural or pericardial nodule(s)  
|               | **M1b**: pulmonary intraparenchymal nodule or distant organ metastasis  |
| **Group Stage** | **I**: T1N0M0  
|               | **II**: T2N0M0  
|               | **IIIA**: T3N0M0  
|               | **IIIB**: T4N0M0  
|               | **IVA**: N1 or M1a  
|               | **IVB**: N2 or M1b  |
Management

- Given rarity, there is no randomized evidence to guide management.
- Resectable tumors (with or without initial biopsy) should proceed to initial resection by a team with experience in the management of thymic neoplasms. [2]
  - Myasthenic symptoms should be managed and optimized prior to resection with immunosuppression, pyridostigmine, and/or IVIG.
- Initially unresectable tumors should first be treated with chemotherapy +/- radiotherapy. [2]
  - Potentially-resectable tumors: chemotherapy → restaging
    - Resectable after restaging: resection +/- PORT
    - Unresectable after restaging: definitive RT +/- chemotherapy
  - Unresectable tumors: concurrent chemoradiotherapy
- Systemic therapy: [2]
  - First-line thymoma: CAP q3 weeks (cisplatin, doxorubicin, cyclophosphamide)
  - First-line thymic carcinoma: Carboplatin/paclitaxel q3 weeks
  - Second-line thymoma: everolimus, octreotide, pemetrexed, gemcitabine
  - Second-line thymic carcinoma: sunitinib, pemetrexed, everolimus, pembrolizumab
  - Concurrent chemotherapy: cisplatin+etoposide or carboplatin+paclitaxel
Management: PORT

• **Controversial.** Given rarity, there is no randomized evidence to guide management. [2-4]
  – **Masaoka stage I, R0:** no PORT
  – **Masaoka stage II, R0:** consider PORT for high-risk features (e.g., large size, WHO type B3/C)
  – **Masaoka stage III:** PORT
  – **Masaoka stage IV:** individualized based on resectability, symptoms
  – **R1-2 resection:** PORT +/- chemotherapy (e.g., for R2 resection or thymic carcinoma)
  – **Thymic carcinoma:** PORT (even if stage I-II)

• **Conflicting evidence for LC, DFS, and OS benefit in different subgroups**
  – **NCDB (PMID: 28126540):** PORT improved OS for Masaoka stage IIB, III, and positive margins. No SS benefit for OS among stage I-IIA [5]
  – **Japanese Consortium (PMID: 25565590):** PORT improved RFS but not OS for stage II-III thymic carcinoma, and did not improve RFS or OS for stage II-III thymoma. [6]
  – **ITMIG (PMID: 27346413):** PORT improved OS in stage II-III R0 thymoma. [7]
  – **Meta-analysis (PMID: 27026316):** PORT improved OS in stage III/IV but not stage II thymoma. [8]
  – All observational series are subject to selection biases in PORT vs. no PORT cohorts.
Management: PORT

- **Treatment planning:** consensus atlas is not available, but reporting guidelines exist [3], with lower inter-rater agreement in postoperative cases relative to definitive cases [9]

- **Radiotherapy:**
  - **Target volumes:** [3]
    - Fuse pre-resection imaging and contour *pre-resection GTV*
    - Postoperative *CTV* encompasses entire surgical bed, clips, anterior mediastinum, and areas of pericardial/pleural contact with the preoperative GTV at risk for microscopic disease. Discussion with surgeon encouraged.
    - Motion-inclusive *ITV* vs. breath hold
    - Elective nodal irradiation not recommended by NCCN
    - *CTV-to-PTV* margin dictated by image-guidance and LINAC
  - **Prescription dose:**
    - R0: 45-50 Gy at 1.8-2 Gy per fraction
    - R1: 54 Gy at 1.8-2 Gy per fraction
    - R2: 60-70 Gy at 1.8-2 Gy per fraction, similar to unresectable disease
    - Hemithoracic RT with boost to high-risk areas is rarely used [3]
  - **Motion management:** inspiration breath hold vs. respiratory gating during treatment to exclude extreme breaths with daily CBCT.

- **Postoperative chemotherapy:** can be considered for thymic carcinoma or R2 resection
Management: Unresectable Disease

- **Potentially-resectable tumors**: induction chemotherapy → resection (if feasible) → risk-adapted PORT [10]

- **Unresectable tumors / R2 resection**: Definitive concurrent chemoradiotherapy [2]
  - **Target volumes (definitive):**
    - Fuse pre-radiotherapy CT/MRI/PET and contour **GTV**
    - No routine **GTV-to-CTV** expansion, but CTV should include areas of pericardial/pleural contact with the GTV at risk for microscopic disease. If chemotherapy precedes radiotherapy, CTV should include pre-chemotherapy extent of disease adapted to anatomy at time of simulation.
    - Motion-inclusive **ITV**
    - Elective nodal irradiation not recommended by NCCN
    - **CTV-to-PTV** margin dictated by image-guidance and LINAC
  - **Prescription dose**: 60-70 Gy at 1.8-2 Gy per fraction
  - **Motion management**: inspiration breath hold vs. respiratory gating during treatment to exclude extreme breaths with daily CBCT
Management: Unresectable Disease

- **Potentially-resectable tumors:** induction chemotherapy → resection (if feasible) → risk-adapted PORT [10]

- **Unresectable tumors / R2 resection:** Definitive concurrent chemoradiotherapy [2]
  - Evidence:
    - Kim et al: phase II trial of 22 patients with unresectable thymoma treated with CAP q 3-4 weeks x 3 → surgical resection (76% R0) → PORT → CAP q 3-4 weeks x 3 [11]
    - Loehrer: phase II trial of 26 patients with unresectable thymoma treated with CAP q 3 weeks x 2-4 → definitive radiotherapy (54 Gy) [12]
    - Fan et al: phase II trial of 56 patients with unresectable thymoma/thymic carcinoma treated with definitive chemoradiotherapy (60 Gy) with concurrent EP q 4 weeks x 2 → adjuvant EP q 4 weeks x 2 [13]

- **Concurrent chemotherapy:**
  - Generally indicated for suitable candidates in the definitive setting
  - Cisplatin+etoposide or carboplatin+paclitaxel
Surveillance

- **NCCN 1.2020**: Chest CT+contrast every 6 months for 2 years, and then annually for 5 years for thymic carcinomas and 10 years for thymomas.
- **Late toxicity**: given long life expectancy in most cases, late toxicities can include pneumonitis, dyspnea, cardiac toxicity, and secondary malignancies.
- **Recurrence**: [2]
  - Most common site of recurrence is along the pleura/pericardium.
  - Nodal recurrence is uncommon, but thymic carcinomas may metastasize to the bone, liver, kidneys, and lymph nodes.
  - Resection of limited pleural/pericardial metastases can lead to long-term disease control, with prognosis associated with WHO Grade. [14]
References

• PORT:
• Unresectable Disease:
• Recurrent Disease:

Please provide feedback regarding this case or other ARROcases to arrocase@gmail.com

June 19, 2020

ASSOCIATION OF RESIDENTS IN RADIATION ONCOLOGY

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