Thymoma: Epidemiology, Clinical presentation / associations and diagnosis

Dr Sarah Sasson
SydPATH Registrar
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Epidemiology of thymoma

- Rare malignancy of thymic epithelium with unknown etiology
- M=F
- Incidence 0.13 /100 000 (Based on USA NCI data)
- Uncommon in children and young adults; incidence rises in middle age and peaks in 7th decade (similar to other malignancies)
- Higher risk in African Americans, Asians and Pacific Islanders

Engels J Thorac Oncol 2010
Epidemiology of thymoma

- Thymoma incidence has declined over time

![Graph showing thymoma incidence over time from 1970 to 2010 with a downward trend.](Engels J Thorac Oncol 2010)

Risk factors for thymoma

- No clear evidence for proposed thymoma risk-factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Evidence supporting reference or statement</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco smoking</td>
<td>Absence of increased risk of thymoma and other solid cancers</td>
<td></td>
</tr>
<tr>
<td>Irradiation</td>
<td>No increased risk following radiation for lung cancer in other patients</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td>0 No data</td>
<td></td>
</tr>
<tr>
<td>Environmental contaminants</td>
<td>0 No data</td>
<td></td>
</tr>
<tr>
<td>Diet and nutrition</td>
<td>0 No data</td>
<td></td>
</tr>
<tr>
<td>Genetic variant</td>
<td>No family history; increased risk among parents, smokers, and individuals with certain, rare syndromes</td>
<td></td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>No increased risk in HIV-infected people or transplant recipients</td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td>Unreported role of infection, and risk for infection, however EBV is likely involved in thymoma-related tumour variants</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EBV, Epstein-Barr virus; HIV, human immunodeficiency virus

*Symbols range from 0 = none (no evidence against reference), to 1 star (weak evidence), to 3 plus signs (strong evidence for reference).*
Risk factors for thymoma

- Little evidence of thymoma following other malignancies (particularly those where treatment involves ionizing radiation to the chest)

| Table 3 |
|---|---|---|
| First malignancy | Thymoma cases, n | Standardized incidence ratio (95% CI) |
| Digestive system | 8 | 1.0 (0.4-2.0) |
| Lung/breaches | 4 | 1.0 (0.1-4.7) |
| Female breast | 14 | 1.3 (0.7-2.2) |
| Non-Hodgkin lymphomas | 2 | 1.4 (0.2-5.1) |
| Hodgkin lymphoma | 1 | 3.6 (0.1-20) |
| Soft tissue/breast | 1 | 3.9 (0.1-21) |
| All sites | 48 | 3.1 (1.6-4.7) |

Data are from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program (www.seer.cancer.gov). SEER 1973-2006: Thymoma risk is evaluated in people who have survived for more than two months after initial cancer diagnosis.

Engels J Thorac Oncol 2010

Thymoma: Pathophysiology

- Most common tumor of the anterior mediastinum
- Primary tumors of the thymus are rare; Of these thymoma is the most common histological subtype
- Thymoma is a neoplasm of thymic epithelia cells. These cells play important role in directing T-cell maturation.
- Histologically thymomas frequently have a rich T-cell infiltrate
- These T-cells have an immature CD4+CD8+ phenotype if the malignancy arises from the thymic cortex
- Occasionally thymomas arise from the thymic medulla, in this case T-cells with have a single CD4+ or CD8+ T-cell phenotype

Kawai and Akira Nat Immunol 2010
Thymoma: Pathophysiology

- When these abnormal cells emigrate they are likely responsible for the autoimmune disorders that often accompany thymoma e.g. myasthenia gravis
- The autoimmunity seen in thymoma is not antigen-specific but similar to patients with GVHD following BMT
- The epithelial cell is the malignant component while the T-cell infiltrate is considered benign
- Classified as benign or malignant based in capsular invasion

Kawai and Akira Nat Immunol 2010

Thymoma: Pathophysiology

- It has been proposed that auto-reactive T-cells in thymoma arise from inappropriate negative selection of CD4+8+ T-cell progenitors due to:
  - Lack of thymic medullary function
  - Low expression of AIRE autoimmune regulator
  - Paucity of BM derived DCs

Fujii Surg Today 2013
Thymoma: Proposed mechanisms for autoimmunity

- Negative selection normally plays an important role in deleting T-cells that bind too strongly to MHC+self-peptide
- Thymus also normally generates T-reg cells
- Peripheral T-cells play a role in promoting B-cell production of antibody

Clinical presentation of thymoma

- Rule of thirds:
  - 1/3 present with myasthenia gravis
  - 1/3 with local symptoms (chest pain, neck mass, SVC obstruction)
  - 1/3 incidental finding on chest radiography
- Associated with indolent growth and a variety of Para neoplastic syndromes
Myasthenia Gravis (MG) and Thymoma

- MG is an autoimmune disease characterised by autoantibodies against AChR causing post-synaptic membrane destruction at neuro-muscular junctions.
- 15-20% of patients with MG have thymic hyperplasia or tumors
- Additionally 25% of thymoma patients who are neurologically asymptomatic have anti-AChR antibody in their serum

Fig. 1 A high proportion of patients with thymoma have anti-AChR antibody in their serum. Studies show that 16.3% of thymoma patients have a clinical diagnosis of myasthenia gravis. All of them are anti-AChR antibody positive. Twenty-six percent of patients with thymoma but without muscle weakness are anti-AChR antibody positive. In total, 38.3% of thymoma patients have serum anti-AChR antibody

Fujii Surg Today 2013
Myasthenia Gravis (MG) and Thymoma

- Removing the thymoma does not guarantee that the patient will be protected from developing MG in the future.
- There are reports of patients with thymoma (MG-AChR Ab-) who develop MG 10 years post-thymectomy.
- Secondary to auto-reactive T-cells already in the periphery

Thymoma and Autoimmunity

- Thymoma has also been associated with other autoimmune diseases possibly secondary to the defective immune regulation.
- 30% of patients with thymoma will be diagnosed with an autoimmune disease concurrently or post-thymectomy.
- 50% are diagnosed concomitantly with 2 autoimmune diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Presence of anti-ACh antibodies</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>MG</td>
<td>Reduced in anti-ACh antibodies</td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>Yes</td>
<td>13, 16, 17</td>
</tr>
<tr>
<td>Sjögren’s</td>
<td>Yes</td>
<td>14, 25, 39</td>
</tr>
<tr>
<td>APS</td>
<td>Yes</td>
<td>13, 47, 48</td>
</tr>
<tr>
<td>Other</td>
<td>Yes</td>
<td>13, 20, 49</td>
</tr>
<tr>
<td>Polyendocrinopathy, periarthritis, urticaria</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>13, 20, 23, 28, 50, 51</td>
<td></td>
</tr>
<tr>
<td>PA, UC, DM, scleroderma</td>
<td>13, 20, 23, 28, 50, 51</td>
<td></td>
</tr>
<tr>
<td>Takayasu syndrome, giant cell disease, reactive arthritis</td>
<td></td>
<td></td>
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Shelly et al Cell & Mol Immunol 2011
Thymoma and Autoimmunity

- 1.5-2% of patients with thymoma are diagnosed with SLE.
  - Some data suggests history of thymoma correlates with steroid-resistant SLE and a worse prognosis
- Acquired pure-red-cell aplasia has also been found in association with thymoma (5%)
  - RBC damage here is apparently T-cell mediated
- Other immune-mediated cytopenias (thrombocytopenia and neutropenia) have been reportedly associated with thymoma
- Thymoma has been associated with Paraneoplastic pemphigus vulgaris and regression of bullous disease has followed thymectomy

Shelly et al Cell & Mol Immunol 2011

Diagnosis of thymoma

- Patients with myasthenia gravis often have a CT chest as part of initial investigations
- Diagnosis usually required core biopsy (FNA often inadequate) and both histopathology and flow cytometry studies are useful
- Classification systems of thymoma have limited ability in predicting course of disease.
- Staging is the best predictor of clinical behavior
- DDx Thymic carcinoma
  - Distinction not clear cut
  - Generally associated with paucity of lymphocytes
  - Often more invasive
  - Associated with decreased survival
- Other DDx lymphoma, carcinoid tumors, germ cell line tumors/ teratomas
Classification of thymoma

Table 1. Adapted from [1] and [2].

<table>
<thead>
<tr>
<th>TYPE</th>
<th>Histopathology</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>A tumor composed of a population of neoplastic thymic epithelial cells having a lymphoid appearance. Tumors are generally characterized by the presence of lymphocytes or plasma cells.</td>
</tr>
<tr>
<td>B1</td>
<td>A tumor characterized by the presence of type A thymoma with admixed lymphocytes.</td>
</tr>
<tr>
<td>B2</td>
<td>A tumor composed of thymic epithelial cells and lymphocytes, with variable amounts of stromal tissue.</td>
</tr>
<tr>
<td>B3</td>
<td>A tumor composed of thymic epithelial cells and lymphocytes, with variable amounts of stromal tissue.</td>
</tr>
</tbody>
</table>

Thymoma: A thymic tumor consisting of thymic epithelial and lymphoid cells. It is a type of epithelial tumor that is characterized by the presence of lymphocytes and plasma cells.

Staging of thymoma

<table>
<thead>
<tr>
<th>STAGE</th>
<th>Criteria of Clinical Staging</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Macrophotically completely encapsulated and microscopically no capsular invasion</td>
</tr>
</tbody>
</table>
| II    | 1. Macrophotic invasion into surrounding fatty tissue or mediastinal pleura  
    2. Microscopic invasion into capsule |
| III   | Macrophotic invasion into neighboring organ, i.e., pericardium, great vessels, or lung |
| IVa   | Pleural or pericardial dissemination |
| IVb   | Lymphogenous or hematogenous metastasis |

Mikhail et al. Curr Oncol Rep 2012
The role of Flow Cytometry in the diagnosis of thymoma

- The anterior mediastinum is a relatively common site for both primary and secondary malignancy
- While histopathology is the mainstay of diagnosis other techniques play a useful role in the diagnostic setting especially taking into account:
  - Limited availability of diagnostic material
  - Crush artifact in small biopsies
  - Need for fast diagnosis (SVC obstruction)
- In a study of 10 patients with anterior mediastinal tumors all underwent fine needle (18G), US guided biopsy and flow cytometry analysis was performed. These results were compared with the histological diagnosis (single-blinded study).

Yokoyama et al. Surg Today 2003

The role of Flow Cytometry in the diagnosis of thymoma

- Flow Cytometry successfully identified 6/6 patients with thymoma and excluded 4/4 with other diagnosis. Threshold was 3% of CD4+8+ DP cells. (Sensitivity 100%; Specificity 100%)
- Histology had a diagnostic sensitivity of 67% and specificity of 100%
- Equitability of Sensitivity and Specificity given Flow cytometry was only being used for 1 diagnosis

Yokoyama et al. Surg Today 2003
The role of Flow Cytometry in the diagnosis of thymoma

- A larger study examined 100 cases of anterior mediastinal tumor sent for flow cytometry
  - Of these 5 (5% had a cell yield too low to phenotype)
- 33/95 had corresponding histopathology reports
- In 11/11 cases of thymoma diagnosis could be made by flow cytometry alone

### Typical Flow Cytometry in thymoma

**Figure 4.** Thymoma. Typical histologic pattern of non-specific lymphocytes and interdigitated epithelial cells (I., x 200, h. x 1,000). The epithelial component is highlighted by antibody immunostaining (a). Flow cytometry (b) reveals an immature T-cell population comprised of two distinct clusters (c) and a B-cell population (d). Flow cytometry (e) reveals a double-tailed comet.
Management of thymoma

Table 4. Practice Guidelines [32]

<table>
<thead>
<tr>
<th>Stage</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Complete surgical resection of thymus and surrounding mediastinal tissue. Best prognosis for fully encapsulated and resectable tumors.</td>
</tr>
<tr>
<td>II</td>
<td>Complete surgical resection as above. Radiation considered for patients with high risk of local recurrence. Surgically inoperable stage I or II disease: Chemo-radiation or radiation for patients medically unfit for surgery.</td>
</tr>
<tr>
<td>III</td>
<td>IIIA: Consider surgery before or after neo-adjuvant chemotherapy with goal of complete excision with wide surgical margins. IIIB: Surgery after neo-adjuvant chemotherapy with maximal debulking if complete resection not possible. Adjunct radiotherapy commonly used.</td>
</tr>
<tr>
<td>IV</td>
<td>IVA: Surgery after neo-adjuvant chemotherapy with maximal debulking if complete resection not possible; if inoperable, chemotherapy concurrent with or sequential to radiation therapy. IVB: Non-surgical management: Radiotherapy in life-threatening situations; Palliative chemotherapy should be considered.</td>
</tr>
</tbody>
</table>

Mikhail et al Curr Oncol Rep 2012

Conclusions

- Thymomas are the most common anterior mediastinal malignancy.
- Represent thymic epithelial cell tumors of unknown etiology.
- Histologically most thymomas contain a CD4+CD8+ T-cell rich infiltrate which appears as a “double tailed comet” on CD4 vs CD8 flow cytometry histograms.
- Thymoma is associated with a number of autoimmune conditions and myasthenia gravis in particular.
- It is likely thymoma-associated autoimmunity results from a dysregulated thymic epithelium and failure of negative selection resulting in emigration of autoreactive immature T-cells into peripheral circulation.
Conclusions

• Classification of disease ranges from early stages of complete encapsulation to thymic carcinoma in which there is a higher incidence of invasiveness and little or no T-cell infiltrate is present.

• The diagnosis of thymoma is classically made by histopathology and more recently by flow cytometry.

• Flow cytometry has a high sensitivity for diagnosis of thymoma and may have added advantages of being able to be run on small sample volumes, pre-open biopsy and/or excision and return results with a fast turn-around time.

• Treatment of thymoma involved surgical resection, chemo and radiotherapy.

Thank you

• Questions?