Thymoma:
Epidemiology, Clinical presentation / associations and diagnosis

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27th June 2014

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

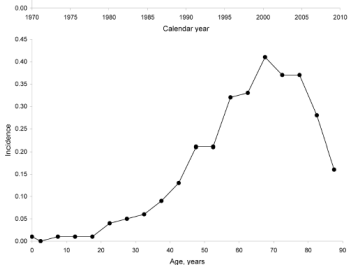
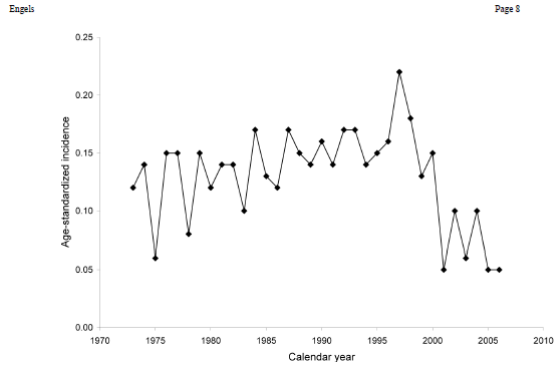


Figure 1. Thymoma incidence in the U.S, according to calendar year and age at diagnosis Panel A shows incidence as a function of calendar year of diagnosis. Incidence is per 100,000 person-years and is standardized to the 2000 U.S. general population. Panel B shows incidence

Engels J Thorac Oncol 2010

Epidemiology of thymoma

- **Thymoma incidence has declined over time**



Engels J Thorac Oncol 2010

Risk factors for thymoma

- **No clear evidence for proposed thymoma risk-factors**

Table 4

Potential risk factors for thymoma

Cancer risk factor	Evidence regarding relevance in thymoma*	Comment
Tobacco/alcohol	-	Absence of increased risk of tobacco and alcohol related cancers.
Ionizing radiation	--	No increased risk following radiation for benign enlarged thymus or other cancers.
Occupation	0	No data
Environmental contaminants	0	No data
Diet and nutrition	0	No data
Genetic variants	+	No family clustering. However, increased risk among Asians/Pacific Islanders, and association with sarcomas, are suggestive.
Immunosuppression	---	No increased risk in HIV-infected people or transplant recipients.
Infections	-	Unconfirmed reports of associations with viral infections. However, EBV is likely involved in lymphoepithelial carcinoma variant.

Abbreviations: EBV Epstein Barr virus, HIV human immunodeficiency virus

*Symbols range from 3 minus signs (strong evidence against relevance), to a zero (no evidence), to 3 plus signs (strong evidence for relevance).

Engels J Thorac Oncol 2010

Risk factors for thymoma

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

Table 3

Risk of thymoma following selected other malignancies in the U.S.

First malignancy	Thymoma cases, n	Standardized incidence ratio (95% CI)
Digestive system	8	1.0 (0.4-2.0)
Lung/bronchus	4	1.8 (0.5-4.7)
Female breast	14	1.3 (0.7-2.2)
Non-Hodgkin lymphoma	2	1.4 (0.2-5.1)
Hodgkin lymphoma	1	3.6 (0.1-20)
Soft tissue/heart	1	3.9 (0.1-21)
All sites	68	1.3 (1.0-1.7)

Data are from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program (www.seer.cancer.gov), SEER9 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

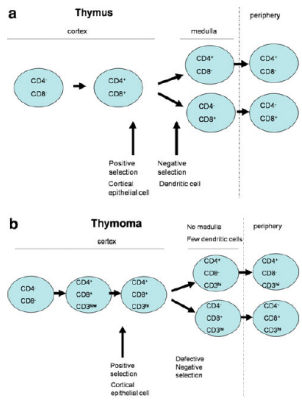
Kawai and Akira Nat Immunol 2010

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

Myasthenia Gravis (MG) and Thymoma

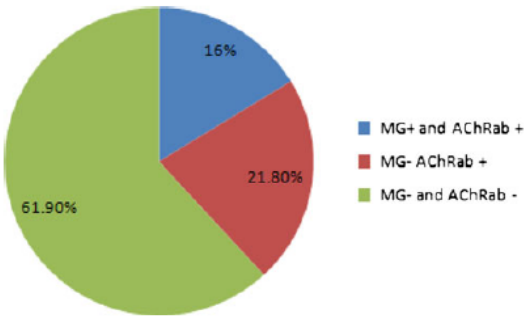


Fig. 1 A high proportion of patients with thymoma have anti-AChR antibody in their serum. Studies show that 16.3 % of thymoma patients have a clinical diagnosis of myasthenia gravis. All of them are anti-AChR antibody positive. Twenty-six percent of patients with thymoma but without muscle weakness are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

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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 2 Autoimmune diseases associated with thymoma

Disease	Remission post-tymectomy	Ref.
MG	Reduction in anti-ACH antibodies	9, 13, 46
SLE	Yes	13, 16, 17
SIADH	Yes	24, 25, 35
ARCA	Yes	13, 47, 48
BP	Yes	13, 26, 49
Others	Unknown	
Polymyositis, pernicious anemia		13, 29, 32, 35, 50, 51
Thyroiditis, hyperthyroidism		13, 29, 32, 35, 50, 51
RA, UC, DM, scleroderma		13, 29, 32, 35, 50, 51
Takayasu syndrome, Graves' disease, encephalitis		13, 29, 32, 35, 50, 51

Abbreviations: ACH, acetylcholine receptor; ACRA, acquired red cell aplasia; BP, bullous pemphigoid; DM, dermatomyositis; MG, myasthenia gravis; RA, rheumatoid arthritis; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SLE, systemic lupus erythematosus; UC, ulcerative colitis.

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 Para neoplastic 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 WHO 1999/2004[41, 41]

TYPE	Histopathology
A	A tumor composed of a population of neoplastic thymic epithelial cells having spindle/oval shape, lacking nuclear atypia, and accompanied by few or no non-neoplastic 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 minor component of lymphocytes, resulting in a sheet like growth of the neoplastic epithelial cells
Thymic Carcinoma	A thymic tumor 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. Thymic carcinomas lack immature lymphocytes; whatever lymphocytes may be present are mature and usually admixed with plasma cells

Mikhail et al Curr Oncol Rep 2012

Staging of thymoma

STAGE	Criteria of Clinical Staging
I	Macroscopically completely encapsulated and microscopically no capsular invasion
II	1. Macroscopic invasion into surrounding fatty tissue or mediastinal pleura
	2. Microscopic invasion into capsule
III	Macroscopic invasion into neighbouring organ, i.e. pericardium, great vessels, or lung
IVa	Pleural or pericardial dissemination
IVb	Lymphogenous or hematogenous metastasis

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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

Table 1. Summary of the patient characteristic data from needle biopsy specimens and the final diagnosis

Case	Age (years)/sex	DP cell	FACS diagnosis	Histological diagnosis of needle biopsy[a]	Histological diagnosis of resected sample[a]
1	56/M	71.2%	Thymoma	Thymoma/mixed/moderate	Thymoma/mixed/moderate
2	32/F	66.0%	Thymoma	Thymoma/polygonal/predominant	Thymoma/mixed/moderate
3	55/M	77.3%	Thymoma	Thymoma/polygonal/moderate	Thymoma/polygonal/moderate
4	30/F	15.9%	Thymoma	Thymoma/mixed/moderate	Thymoma/mixed/moderate
5	47/M	68.4%	Thymoma	Thymoma/polygonal/predominant	Thymoma/polygonal/predominant
6	64/M	46.7%	Thymoma	Thymoma/mixed/moderate	Thymoma/mixed/moderate
7	61/M	0.6%	Other disease	Thymoma/polygonal/scant	Thymic carcinoma (SqCC)
8	30/M	0.4%	Other disease	s/o Thymoma/mixed/moderate	Seminoma
9	29/M	0.2%	Other disease	s/o Thymoma/polygonal/moderate?predominant	Seminoma
10	18/M	0.2%	Other disease	Normal thymus	Hodgkin disease (NS type)

DP, double positive; FACS, fluorescence-activated cell sorting; s/o, suggestive of; NS, nodular sclerosis; SqCC, squamous cell carcinoma
[a]Diagnosis/epithelial type/relative lymphocyte abundance

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

TABLE I Histologic diagnoses in 100 cases of mediastinal tumors

Diagnosis	Number of cases	Flow cytometry positive	Flow cytometry negative	Flow cytometry not diagnostic
B-cell lymphoma (total)	34	31	1	2
Diffuse large B-cell lymphoma	21	18	1	2
Follicular lymphoma	6	6	0	0
B-cell SLL/CLL	5	5	0	0
Mantle cell lymphoma	1	1	0	0
Marginal zone lymphoma	1	1	0	0
Peripheral T-cell lymphoma	3	2	1#	0
Metastatic carcinoma	10	7	2	1
Hodgkin lymphoma	12	0	11	1
Precursor T-lymphoblastic leukemia/lymphoma	8	7	0	1
Thymoma/thymic hyperplasia	11	11**	0	0
Benign*	22	0	22	0

*other than thymic tissue.
#anaplastic large cell lymphoma.
**flow cytometry revealed an immature T-cell population.

Gorczyca et al Leuk & Lymph 2004

Typical Flow Cytometry in thymoma

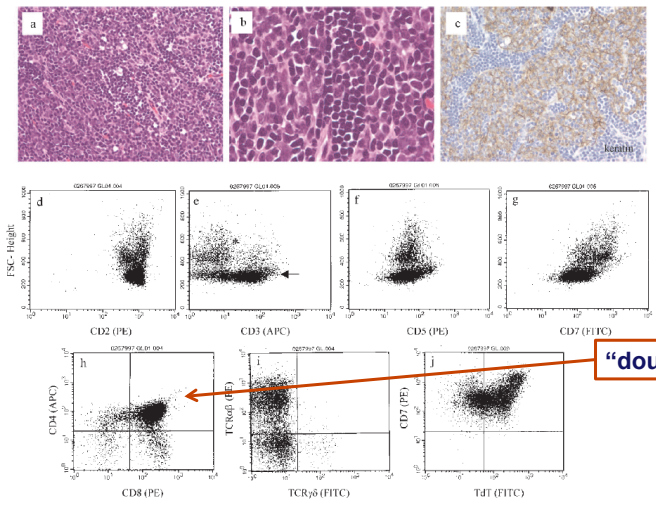

FIGURE 4 Thymoma. Typical histologic pattern of immature lymphocytes and intermixed epithelial cells (a, × 200; b, × 1,000). The epithelial component is highlighted by keratin immunostaining (c). Flow cytometry (d–j) revealed an immature T-cell population comprised of two distinct subsets: small lymphocytes with variable expression of surface CD3 (arrow, e) and larger cells (*) with negative sCD3. Note dual CD4/CD8 expression (h) and positive expression of TCRαβ (i) and TdT (j).

Gorczyca et al Leuk & Lymph 2004

Management of thymoma

Table 4 Practice Guidelines [32]

Stage	Management
I	Complete surgical resection of thymus and surrounding mediastinal tissue
	Best prognosis for fully encapsulated totally resected tumors
II	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
III	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
	Adjuvant radiotherapy commonly used
IV	IVA: Surgery after neo-adjuvant chemotherapy with maximal debulking if complete resection is 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

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 my histopathology and more recently 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?