62 year old woman with a mediastinal mass

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Clinical Presentation

• 62 year old woman who initially presented with fatigue, weight loss, and shortness of breath
• Was found to have a right pleural effusion and extensive lymphadenopathy
• Inguinal lymph node biopsy was performed

Disclosure of Relevant Financial Relationships

Dr. Julia T Geyer declares she has no conflicts of interest to disclose.

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Inguinal lymph node work up

- Immunophenotype: CD20+, CD10+, BCL2+, BCL6+ tumor cells
  - Kappa light chain restriction
  - Ki67 proliferation rate of 5%
- Cytogenetics:
  - 47~50,XX,+X,add(1)(p36.1),del(4)(q12q22),del(5)(q15q31),
    inv(17)(p13q21),del(13)(q14q22),
    +16,add(17)(p13)
  - FISH: IGH-BCL2 gene rearrangement in 80% of interphase nuclei
- Diagnosis: Follicular lymphoma, grade 1 of 3
- Staging bone marrow biopsy: involvement by low-grade follicular lymphoma, consistent with stage IV disease

Clinical Presentation, continued

- The patient was treated with 6 cycles of chemotherapy
- 10 months later, at the completion of planned treatment, surveillance PET/CT identified a new right anterior mediastinal mass
  - It measured 9.5 x 5.0 cm with associated maximum SUV of 9.3
  - Excisional biopsy of the mediastinal mass was performed
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Mediastral mass work up

- Immunohistochemistry: CD20+, CD10+, BCL2+, TdT+ tumor cells
  - Tumor cells negative for BCL6, CD34, CD99, cytokeratin, EBER, immunoglobulin light chains
  - Ki67 proliferative fraction >90%
- FISH: IGH-BCL2 gene rearrangement in 90% of nuclei
- FISH: C-MYC gene rearrangement in 98% of nuclei
- Comparative PCR: same distinct monoclonal B-cell population present in the inguinal lymph node and mediastinal mass
- Final diagnosis ???

The differential diagnosis of a mediastinal mass

- Mediastinal mass / lymphadenopathy is a frequent indication for surgical biopsy
- The anterior mediastinum is the most common location of mediastinal masses in adults:
  - Thymic mass represents ~50% of all cases
  - Thymoma, thymic carcinoma, thymic cysts
  - Germ cell tumor
  - Medastinum is the most common location for extragonadal germ cell tumors in adults
  - Enlarged or ectopic thyroid
  - Lymphoma
  - T-lymphoblastic lymphoma
  - Primary mediastinal (thymic) large B cell lymphoma
  - Classical Hodgkin lymphoma
  - Extramedullary marginal zone lymphoma

The differential diagnosis of a mediastinal mass

- Patients with mediastinal lymphomas may present with:
  - Systemic symptoms
  - Local symptoms due to compression of mediastinal structures
- The diagnosis of mediastinal lymphoma may be challenging
  - Fine needle aspirates usually do not provide sufficient tissue for lymphoma subtyping
  - Core biopsy can be inadequate (morphology, flow cytometry, immunohistochemistry, cytogenetics)
  - Small biopsies may be non-diagnostic due to crush artifact or extensive necrosis, fibrosis, or cystic change
  - Definitive histologic diagnosis of nodular sclerosis Hodgkin lymphoma can be particularly difficult due to fibrosis, crush artifact and scant number of neoplastic cells
T-lymphoblastic lymphoma

- Most patients are adolescent and young adult men
- Patients present with rapidly enlarging mediastinal mass and/or peripheral lymphadenopathy
  - Rapid growth of the mass may present a respiratory emergency
  - Frequently associated with pleural effusions
- The term lymphoma is used if there is mass lesion with minimal peripheral blood / bone marrow involvement
- T-lymphoblastic leukemia is a more appropriate term if there is high WBC and significant marrow involvement

- Immunophenotype:
  - Tumor cells are usually positive with CD3, CD7 and TdT
  - Variable expression of other T-cell markers (CD2, CD4, CD5, CD8) and immature markers (CD34, CD1a, CD99, CD10)

- Genetics:
  - Karyotype: >60% of patients have an abnormal karyotype
  - FISH: ~30% have chromosomal translocations involving the TCR loci (chromosomes 7q34 and 14q11)
  - NOTCH1 is the most commonly mutated oncoprotein in T-ALL (>50% of all cases)
Extranodal MALT lymphoma

- Thymic MALT lymphoma is rare (~35 reported cases)
- Almost exclusively reported in Asian female patients with a median age of ~50 years
- Strong association with autoimmune disease, especially Sjögren’s syndrome
- Most patients have either serum M-spike or polyclonal hypergammaglobulinemia
- Mediastinal mass is usually an incidental finding

Extranodal MALT

- Morphology: scattered reactive lymphoid follicles surrounded by neoplastic small marginal zone lymphocytes with irregular nuclei and abundant clear cytoplasm admixed with immunoblasts
- Thymic MALT is characterized by epithelial thymic cysts and lymphoepithelial lesions
- Numerous plasma cells are part of the neoplastic clone
- Immunophenotype: tumor cells are mature B lymphocytes that express CD19 and CD20 and are negative for CD5, CD10 or CD23
- Cases with plasmacytic differentiation have monotypic light chain expression by the plasma cells; almost always IgA positive
- Genetics: monoclonal rearrangement of the immunoglobulin heavy chain gene

Primary mediastinal (thymic) large B cell lymphoma

- Separate entity in both REAL and WHO Classifications due to its characteristic features
- Presents in young women
- Typically locally invasive bulky anterior mediastinal mass
- Frequent airway compromise and superior vena cava syndrome
- Frequent direct extension to the lungs, pleura, and pericardium
- ~50% of the patients have a pleural or pericardial effusion
- Up to 50% of the patients have B symptoms
- Morphology: large neoplastic cells with variable nuclear features often with abundant pale cytoplasm commonly associated with delicate interstitial fibrosis
- Immunophenotype: tumor cells are mature B lymphocytes that express CD19 and CD20
  - Characteristically positive for CD23 and CD30 (weak and heterogeneous)
  - Tumor cells may also express MUM1, BCL6 and BCL2
- Genetics: monoclonal rearrangement of the immunoglobulin heavy chain gene
Classical Hodgkin lymphoma

- Morphology: Reed-Sternberg cells and variants (including lacunar cells) in a characteristic polymorphous background
  - Nodular sclerosis CHL has a nodular growth pattern with thick fibrous bands, which surround at least one nodule
  - The number of neoplastic cells is highly variable and can be very scant
- Immunophenotype: tumor cells express Pax-5, CD30 (strong diffuse staining), CD15 and are negative for CD45 and CD20
- Genetics: non contributory

- Patients present with fatigue, retrosternal chest pain, dyspnea, or cough
- 30% to 50% of patients with mediastinal CHL are asymptomatic
- Nodular sclerosis CHL is the most common subtype involving anterior mediastinum and/or mediastinal lymph nodes (>95% of cases)
Back to the patient...

- Recent history of low-grade follicular lymphoma treated with chemotherapy
- New, rapidly growing mediastinal mass has certain similarities with the previously diagnosed disease
  - CD10-positive B cell lymphoma
  - Evidence of IgH-BCL2 gene rearrangement
  - Identical IgH gene rearrangement (same clonal origin)
- It also has several key differences
  - Blastoid morphology with numerous mitotic figures and high Ki67 proliferation rate
  - Expression of TdT (immature marker)
  - Loss of CD20 and light chain expression (suggestive of immature B cells)
  - Newly acquired c-MYC gene rearrangement

Final diagnosis

- B-lymphoblastic leukemia / lymphoma arising from a clonally related follicular lymphoma

Follicular lymphoma

- FL is the most common lymphoma in the US and in Western Europe
- It is a tumor of mature germinal center B lymphocytes
- Usually occurs in middle-aged individuals and the elderly
- Is characterized by the presence of t(14;18); IgH-BCL2 gene rearrangement (~65% of the patients)

Follicular lymphoma, transformation

- FL is a very indolent lymphoma
  - Cumulative risk of transformation is 3% per year
- By far, the most common type of transformation is to diffuse large B-cell lymphoma (DLBCL)
- Other rare types of transformation include:
  - B cell lymphoma with features intermediate between DLBCL and Burkitt lymphoma (gray zone lymphoma)
  - Double-hit lymphoma (BCL2 and MYC gene rearrangements)
  - Plasmablastic lymphoma
  - B-lymphoblastic lymphoma (B-ALL)

Lymphoblastic transformation of follicular lymphoma

- ~20 cases described in the literature
- How can patients with a follicular lymphoma develop a clonally-related acute leukemia?
- It has been widely assumed that lymphoid neoplasms correspond to normal counterparts in lymphoid development
Follicular lymphoma

- The t(14;18) translocation of follicular lymphoma appears to occur in bone marrow at the earliest stages of B cell development.
- The common progenitor cell (CPC) hypothesis suggests that CPC resides in the bone marrow stem cell niche from where it migrates to the periphery.
- Sequencing studies of DLBCLs arising from FL appear to support the CPC hypothesis.
- CPCs may survive chemotherapy and allow for selection of more aggressive subclones.

B cell dedifferentiation: in vitro mature B cells can be reprogrammed into uncommitted hematopoietic progenitors.

Transdifferentiation and lineage plasticity: a number of reports of mature B cell lymphoma transforming into clinically related histiocytic sarcoma, interdigitating cell sarcoma, Langerhans cell tumors.
The significance of MYC rearrangement

- MYC translocation is a key event in high-grade transformation of B-cell lymphoma and multiple myeloma
- The updated 2016 WHO Classification of Hematopoietic Tumors has a new category of “high-grade B cell lymphoma with MYC and BCL2 gene rearrangements”
  - Includes cases previously diagnosed as “double hit lymphoma” and “B-cell lymphoma undistinguishable with features intermediate between DLBCL and Burkitt lymphoma”
  - Usually de novo
  - Morphology / immunophenotype more aggressive than typical DLBCL
  - Has a very poor prognosis, and appears refractory to R-CHOP
  - The WHO specifically excludes cases of follicular lymphoma or lymphoblastic lymphoma

Patient, clinical follow up

- Treated with hyper CVAD and achieved complete remission
- Underwent allogeneic stem cell transplant 4 months after diagnosis of transformation
- Multiple complications post transplant
- New hypermetabolic mediastinal mass 6 months post transplant
- Biopsy: relapsed B-lymphoblastic lymphoma
- Patient died of disease 10 months after the diagnosis of transformation
THANK YOU