HODGKIN'S LYMPHOMA

Background

1. Definitions:
    - Hodgkin's Lymphoma is a malignancy of lymphatic cell line origin
2. General Information
    - Hodgkin's Lymphoma
        - Characterized by Reed-Sternberg cells[1]
            - Preapoptotic, germinal center B cell that has lost B-cell phenotype
            - "master regulator" of inflammatory process
        - Types[2]
            - Classical
                - Nodular sclerosing
                - Lymphocyte-rich
                - Mixed-cellularity
                - Lymphocyte-depleted
            - Nodular lymphocyte-predominant[3,4]
                - Uncommon
                - Low grade monoclonal B-cell lymphoma
                - Can transform to diffuse, large B-cell lymphoma

Pathophysiology

1. Pathology of Disease
    - Genetic modifications during B-cell development in the bone marrow lead to DNA alterations that may become pathologic
2. Incidence, Prevalence (U.S.)[5]
    - Incidence: 3.1/100,000 men, 2.6/100,000 women
        - Bimodal incidence pattern[4]
            - Peak between ages 15-34
            - Peak in ages above 60
        - ~ 8800 new cases diagnosed annually
    - Prevalence: ~ 167,000 (2008)
3. Risk Factors[6]
    - Associated factors include familial, viral disease and immune suppression
4. Morbidity / Mortality
    - Morbidity
        - Generally treatment-related (see below)
    - Mortality
        - 5-year survival rate greater than 90%[3]

Diagnostics[4,6]

1. History
    - "B symptoms"
        - Unexplained fever
        - Night sweats
        - Recent weight loss

- Adenopathy

2. Physical Examination
   - Painless lymphadenopathy
     - Freely moveable with rubbery consistency
     - Hodgkin's
       - Predictable contiguous spread
       - Splenic involvement ~25% of the time
3. Diagnostic Testing
   - Biopsy
     - Large surgical specimen
     - Excisional lymph node biopsy
       - Inguinal, axillary nodes generally avoided due to increase likelihood of revealing "reactive changes"
       - Fine Needle Aspiration unreliable[7]
   - Bone marrow aspiration
     - Unlikely to be positive in absence of B symptoms or subnormal blood cell line counts (under 0.5%)
4. Laboratory evaluation
   - Obligatory
     - CBC, ESR, glucose level, alkaline phosphatase, lactate dehydrogenase (LDH,) liver enzymes, albumin, TSH
   - Compulsory
     - Hepatitis B, hepatitis C, HIV screening
5. Diagnostic imaging
   - Mandatory
     - Chest x-ray, chest and abdominal CT scan
   - Optional
     - PET scan - can detect disease not seen with other imaging modalities
6. Other studies
   - Mandatory
     - Cardiac function test
     - Pulmonary function test
   - Optional
     - ENT consult
     - Reproductive consult
7. Diagnostic Criteria
   - Lymph node or extranodal tissue biopsy showing "Reed-Sternberg" cells within appropriate cellular environment for diagnosis
   - Staging (based on involved sites, lymph nodes affected on one or both sides of diaphragm, bulky disease, contiguous or disseminated extranodal involvement, presence of "B" symptoms)
     - Stage I
       - Single lymph node region or one extranodal site
     - Stage II
       - Two or more lymph node regions, same side of diaphragm (II)
       - Local extralymphatic extension plus one or more lymph node regions on same side of diaphragm (IIE)

- Stage III
  - Lymph node regions, both side of diaphragm (III)
  - If accompanied by local extralymphatic extension (IIIE)
- Stage IV
  - Diffuse involvement of one or more extralymphatic organs or sites
- Subclassification
  - A - absence of "B" symptoms
  - B - Presence of at least one of the following:
    1. Wt loss (> 10% from baseline 6 months prior to staging)
    2. Recurrent fever (> 100^0F)
    3. Recurrent night sweats

Differential Diagnosis

1. Key Differential Diagnoses
   - Malignancies: Leukemias, Metastases of Unknown Primary
   - Infectious Disease: Cat Scratch Disease, Cytomegalovirus, HIV, Mononucleosis
   - Miscellaneous: Sarcoidosis, Kawasaki's Disease
2. Extensive Differential Diagnoses
   - Medications: Allopurinol, Atenolol, Captopril, Carbamazepine, Hydralazine, Penicillins, Phenytoin, Primidone, Quinidine, Trimethoprim/Sulfamethoxazole, Sulindac
   - Serum Sickness

Therapeutics[6]

1. Classic Hodgkin's Lymphoma
   - Limited Stage
     - Brief Chemotherapy followed by Radiotherapy
     - 2 or 3 cycles of ABVD (Adriamycin, Bleomycin, Vincristine, Dacarbazine) followed by 30 Gy involved-field radiotherapy (IF-RT)
   - Intermediate Stage
     - 4 cycles of ABVD followed by 30 Gy IF-RT
     - Other more intensive regimens being evaluated for healthy patients under age 60
   - Advanced Stage
     - Chemotherapy alone
       - 6 to 8 cycles of ABVD (SOR:C)[4] or 8 cycles of BAECOPP escalated(Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone, G-CSF)
       - BAECOPP escalated should not be used in patients over 60 years old due to increased toxicity
     - Radiotherapy only for large residual masses
   - Relapsed Classic Hodgkin's Lymphoma
     - High-dose chemotherapy followed by Autologous Stem Cell Transplantation (ASCT)

- Refractory or Relapsed Classical Hodgkin's
  - Primary cause of death if diagnosed within 10-15 years after initial treatment[4]
  - High dose chemotherapy followed by autologous stem cell transplant treatment of choice
  - Salvage regimens given to reduce tumor size and mobilize stem cells prior to high-dose chemotherapy and autologous stem cell transplant
  - No treatment standard for patients relapsing after high-dose chemotherapy and stem cell transplant

2. Nodular Lymphocyte Predominant Hodgkin's Lymphoma (NLPHL)
   - Stage IA without risk factors
     - 30 Gy IF-RT alone
   - Other Stages
     - Treated same as Classic Hodgkin's Lymphoma with exception of stage IA
   - Relapsed Nodular Lymphocyte-predominant Hodgkin's Lymphoma
     - Obtain biopsy in those suspected of relapse (transformation to aggressive Non-Hodgkin's Lymphoma needs to be excluded)
     - Localized relapses of NLPHL can be treated with rituximab alone
     - Advanced relapses require aggressive salvage therapy + rituximab
3. Hodgkin's Lymphoma Response Evaluation
   - Early/Intermediate Stage: initiated at completion of chemotherapy prior to radiotherapy
   - Advanced Stage: initiated after four cycles of chemotherapy
   - Final staging after completion of therapy
     - Physical exam, lab analysis (CBC with diff, ESR and blood chemistries) and CT scans mandatory (controversial)
       - Early Stage recurrence rate 10% + 80% of recurrences diagnosed by patient or examining provider[8]
     - Advanced stage: FDG-Positron Emission Tomography (PET) helps identify poor-risk individuals
       - Therapy should not be based on results until further clinical trials conducted
       - False-positive PET scan must be excluded
   - Response after relapse is measured in same fashion as initial response

Follow-Up

1. Return to Office
   - Follow up protocols vary:
     - European Society for Medical Oncology (ESMO) recommends[6]:
       - Every 3 months for 1st 6 months, then every 6 months until 4th year, yearly thereafter:
         - History, Physical Exam, Laboratory analysis (CBC with differential, ESR, Chemistries), Chest imaging (CT or CXR) (SOR:C)[4]
         - TSH after neck irradiation (1,2, and 5 years out) (SOR:C)[4]

        - Testosterone/estrogen in younger patients receiving intense chemotherapy
        - CT and other abnormal radiographic tests must be repeated to confirm remission
- Most relapses occur within 5 years of initial treatment
    - 55% suspected on symptom history, 23% found on CXR/CT, 14-18% detected by physical exam[9]
        - Role of Position Emission Tomography in detecting relapse is unclear
    - Usually found by complaint of a new lump[4]
        - Fever, weight loss, night sweats, cough and pain may also be presentation of relapse
- Long-term complications[4,8]
    - Breast cancer - associated with radiation therapy
        - most at risk if radiation received under 35 years of age or if high dose radiation used
        - Long latency period of 10-15 years prior to development
        - Mammogram effective screening tool
        - American Cancer Society recommends yearly Breast MRI in addition to mammography for patients with chest irradiation prior to age 30
        - Premature menopause has protective effect
    - Lung cancer - associated with radiation and chemotherapy
        - Older alkylating agents cited as causative in dose dependent manner (procarbazine, mechlorethamine, dacarbazine)
        - Smoking cessation should be emphasized at time of diagnosis
        - Median survival of lung cancer after Hodgkin's Lymphoma patients is under 1 year
    - Other malignancies due to chemotherapy regimens:
        - Acute Myeloid Leukemia - 1-3% incidence, usually within 10 years of treatment
            - Older Alkylating agents main risk
            - Wide field radiation (uncommon today)
            - ABVD regimen lowers risk
        - Myelodysplatic Syndromes
    - Cardiovascular complications
        - Coronary Artery Disease (CAD) - primary contributor to excess cardiac mortality after therapy
            - Main risk factor - mediastinal radiation
            - Doxorubicin also cardiotoxic
        - Cardiomyopathy - Doxorubicin
            - Female, Cumulative high dose, Younger age at exposure and increased time from exposure
        - Pericardial disease
        - Valvular abnormalities
        - Conduction disturbances

- Reproductive problems (increase with age at treatment)
    - Ovarian failure - higher risk with abdominopelvic radiation therapy and older alkylating agents
    - Infertility
        - Men - spermatogenesis affected by alkylating agents and cyclophosphamide
        - ABVD regimen has lowered male infertility
        - Radiation contributes to damage
        - Consider cryopreservation of sperm prior to treatment
- Other Late Complication of Therapy
    - Thyroid abnormalities - primarily hypothyroidism
        - Irradiation to neck and upper mediastinum increases risk
        - Risk greatest first 5 years after therapy
        - Can occur 20 years after therapy
        - Evaluate thyroid function 1,2, and 5 years after treatment in those status post neck irradiation
    - Dental problems - primarily related to oropharyngeal radiation induced decrease in salivation
        - Preventive dentistry recommended
    - Pulmonary dysfunction
        - Radiation dose and lung volume exposed dependent
        - Bleomycin associated pulmonary fibrosis (common after doses greater than 200 Units per m^2)
    - Fatigue - related to cardiac, pulmonary, thyroid disease

Prognosis

1. Hodgkin's Lymphoma[6]
    - 80-90% of treated patients secure permanent remission and should be considered cured
    - 15% of patients with early disease will relapse[1]
    - 1/3 of patients with advance disease will relapse[1]

Prevention

1. Post Therapy - annual influenza and appropriate interval pneumococcal immunizations recommended

Patient Education

1. The Leukemia and Lymphoma Society
    - http://www.lls.org/diseaseinformation/lymphoma/
2. National Cancer Institute
    - http://www.cancer.gov/cancertopics/types/hodgkin

References

1. DeVita VT, Costa J. Toward a Personalized Treatment of Hodgkin's Disease (Editorial). NEJM 2010; 362(10): 942-3.
2. Lee AI, LaCasce AS. Nodular Lymphocyte Predominant Hodgkin Lymphoma. The Oncologist 2009;14:739-751.
3. Armitage, JO. Early-Stage Hodgkin's Lymphoma. NEJM 2010; 363(7): 653-62.
4. Glass C. Role of the Primary Care Physician in Hodgkin Lymphoma. Amer Fam Phys 2008;78(5):615-22, 625-6.
5. National Cancer Institute Surveillance Epidemiology and End Results. http://seer.cancer.gov/statfacts/html/hodg.html. accessed January 26, 2012.
6. Eichenauer DA, Engert A, Dreyling M. Hodgkin's Lymphoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. Ann Onc 2011; 22(Supp 6): vi55-vi58.
7. Ansell SM, Armitage JO. Management of Hodgkin Lymphoma. Mayo Clnc Proc 2006;81(3):419-26.
8. Juweid ME, Vose JM. Imaging in Early-Stage Hodgkin's Lymphoma. [editorial] NEJM 2010; 362(10): 962.
9. Ng A, et al. Expert Panel on Radiation Oncology-Hodgkin's Lymphoma: Appropriateness Criteria follow-up of Hodgkin's Lymphoma [online publication] American College of Radiology 2010; 10 pages.

Authors: James W. Haynes, MD, & Stephen Greer MSIII, *University of TN COM*

Editor: Robert Marshall, MD, MPH, MISM, CMIO, *Madigan Army Medical Center, Tacoma, WA*