HODGKIN’S LYMPHOMA

Background
1. Definitions:
   o Hodgkin’s Lymphoma is a malignancy of lymphatic cell line origin
2. General Information
   o Hodgkin’s Lymphoma
     ▪ Characterized by Reed-Sternberg cells¹
       • Preapoptotic, germinal center B cell that has lost B-cell phenotype
       • “master regulator” of inflammatory process
     ▪ Types²
       • Classical
         o Nodular sclerosing
         o Lymphocyte-rich
         o Mixed-cellularity
         o Lymphocyte-depleted
       • Nodular lymphocyte-predominant³,⁴
         o Uncommon
         o Low grade monoclonal B-cell lymphoma
         o Can transform to diffuse, large B-cell lymphoma

Pathophysiology
1. Pathology of Disease
   o Genetic modifications during B-cell development in the bone marrow lead to DNA alterations that may become pathologic
2. Incidence, Prevalence (U.S.)⁵
   o Incidence: 3.1/100,000 men, 2.6/100,000 women
     ▪ Bimodal incidence pattern⁴
       • Peak between ages 15-34
       • Peak in ages above 60
     ▪ ~ 8800 new cases diagnosed annually
   o Prevalence: ~ 167,000 (2008)
3. Risk Factors⁶
   o Associated factors include familial, viral disease and immune suppression
4. Morbidity / Mortality
   o Morbidity
     ▪ Generally treatment-related (see below)
   o Mortality
     ▪ 5-year survival rate greater than 90%³

Diagnostics⁴,⁶
1. History
   o “B symptoms”
     ▪ Unexplained fever
     ▪ Night sweats
     ▪ Recent weight loss
2. Physical Examination
   o Painless lymphadenopathy
     - Freely moveable with rubbery consistency
     - Hodgkin’s
       - Predictable contiguous spread
       - Splenic involvement ~25% of the time

3. Diagnostic Testing
   o 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
   o Bone marrow aspiration
     - Unlikely to be positive in absence of B symptoms or subnormal blood cell line counts (under 0.5%)

4. Laboratory evaluation
   o Obligatory
     - CBC, ESR, glucose level, alkaline phosphatase, lactate dehydrogenase (LDH), liver enzymes, albumin, TSH
   o Compulsory
     - Hepatitis B, hepatitis C, HIV screening

5. Diagnostic imaging
   o Mandatory
     - Chest x-ray, chest and abdominal CT scan
   o Optional
     - PET scan - can detect disease not seen with other imaging modalities

6. Other studies
   o Mandatory
     - Cardiac function test
     - Pulmonary function test
   o Optional
     - ENT consult
     - Reproductive consult

7. Diagnostic Criteria
   o Lymph node or extranodal tissue biopsy showing "Reed-Sternberg" cells within appropriate cellular environment for diagnosis
   o 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)
1.30.12

- 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°F)
    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

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)
1. Refractory or Relapsed Classical Hodgkin’s
   - Primary cause of death if diagnosed within 10-15 years after initial treatment
   - 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
     - 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:
       - 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)
         - TSH after neck irradiation (1, 2, and 5 years out) (SOR:C)
- 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
    - Role of Position Emission Tomography in detecting relapse is unclear
  - Usually found by complaint of a new lump
    - Fever, weight loss, night sweats, cough and pain may also be presentation of relapse

- Long-term complications
  - 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
    - Myelodysplastic 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)
  o Ovarian failure - higher risk with abdominopelvic radiation therapy and older alkylating agents
  o 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
  o 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
  o Dental problems - primarily related to oropharyngeal radiation induced decrease in salivation
    ▪ Preventive dentistry recommended
  o Pulmonary dysfunction
    ▪ Radiation dose and lung volume exposed dependent
    ▪ Bleomycin associated pulmonary fibrosis (common after doses greater than 200 Units per m²)
  o Fatigue - related to cardiac, pulmonary, thyroid disease

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

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

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


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