HODGKIN'S LYMPHOMA (HODGKIN'S DISEASE)

LYMPHOMAS

GENERAL

- One of the most curable and treatable malignancy
- Diverse group of disorders
- Lymphoma biology and management has led to several major breakthroughs in cancer treatments
- Lymphoma incidence is increasing
- About 79,000 new cases with 20,000 deaths from lymphoma in 2013 per ACS estimate

HODGKIN'S LYMPHOMA (HODGKIN'S DISEASE)

GENERAL

- About 10% of total lymphoid neoplasms
- B cell neoplasm
- Characteristic cell is Sternberg Reed cell
- Disease spread is generally contiguous
- Exploratory laparotomy and splenectomy are no longer used for staging
- Over 75% of cases are potentially cured

INCIDENCE

- In United states of America:
- About 9200 cases annually (2013 estimate)
- About 1180 deaths annually(2013 estimate)

RISK FACTORS AND ETIOLOGY

- Etiology is unknown
- Risk of HD is increased 3 fold in people with history of infectious mononucleosis
- Risk is increased in AIDS – more extra nodal site involvement and aggressive disease with poor outcomes
- In bone marrow transplant patients
- Increased incidence in wood workers, farmer and meat processors
- No clear cut environmental factors indentified.
- Association with EB virus
- Risk of HD is increased 3 fold in people with history of infectious mononucleosis

PATHOGENESIS

- About half of Hodgkin nodes show evidence of EBV DNA in Stenberg reed cells genome

- Not all Hodgkin's cases are EBV positive.

PREVENTION STRATEGY

- Unknown

SCREENING

- Not available

SYMPTOMS / SIGNS

- Seen in young patients
- Pain less lymphadenopathy Splenomegaly
- Fever, drenching night seats, weight loss, pruritus
- Pain in nodal area after alcohol consumption

DIAGNOSIS

- Requires biopsy: Large atypical lymphoblast surrounded by an infiltrate of inflammatory and accessory cells
- Sternberg Reed cells

HISTOLOGY

- Sternberg Reed cells express CD 15 and CD 30
- WHO classification:
- Classical Hodgkin's lymphoma – 95% of all cases
    - Nodular sclerosis: About 60% of classical Hodgkin's lymphoma
        - Anterior mediastinal mass at presentation
    - Mixed cellularity
        - more common in men
        - About 20% of classical Hodgkin's lymphoma
        - EBV genomic DNA seen in 60-70% of this subtype - Disseminated disease is more common
    - Lymphocyte rich classic Hodgkin's lymphoma
        - More common in elderly men and present at early stage
        - Cells have feature similar to mantle cells
        - Late relapses are less common but more commonly fatal when occurs
    - Lymphocyte depleted
        - Less than 5% cases
        - More common in elder men and with HIV infection
        - Higher incidence of abdominal adenopathy, marrow involvement and hepato-splenomegaly
- Nodular Lymphocyte predominant Hodgkin's lymphoma -About 5% of total cases
    - Large neoplastic B cells (popcorn cells)- negative for CD 15 and CD 30
    - Typically seen in men with localized adenopathy – stages I or II and slow progression and prolonged survival

STAGING SYSTEM

Ann Arbor staging

- Stage I: Involvement of single lymph node region or lymphoid structue
- Stage II: Involvement of two or more lymph node regions confined to same side of diaphragm
- Stage III: Involvement of two or more lymph node regions on both sides of diaphargm
- Stage IV: Dissemintated disease (marrow, liver etc)
- Substages:
    - A: Absence of B symotms;
    - B: Presence of B symtoms (fever over 37*C on two ocassions not related to infection. unintended loss of more than 10% body wieght within six months, drenching night sweats)
    - E: Extra nodal site involvement by direct extension of a node

STAGING WORK UP AND OTHER TESTING

- History and physical examination
- Excisional lymph node biopsy with histology and immune phenotype
- CBC diff, Liver enzyme testing, LDH, Sed rate
- Chest x-ray or CT chest
- CT abdomen and pelvis
- PET scan
- Bone marrow aspiration and biopsy (if advanced stage or B symptoms)
- Fertility preservation evaluation if applicable
- Pulmonary function testing
- Cardiac ejection fraction tests
- HIV testing
- Vaccination if splenectomy is planned or splenic RT is given

PROGNOSTIC FACTORS:

- International prognostic Score (IPS)
    - Age over 45 years
    - Male sex
    - Stage 4 disease
    - Serum albumin below 4
    - Hemoglobin below 10.5
    - WBC over 15000,
    - Lymphocytes less than 600 or lymphocyte counts less than 8%
- 5 year survival;
    - Three or more factors: 55%
    - Up to two factors: 74%
    - IPS is not perfect
- FDG PET scan after two cycles of ABVD might be superior predictor than IPS

FDG PET scan in Hodgkin's disease

- Used for
  - Initial staging
  - To assess response to treatment
  - To evaluate residual masses
  - To predict risk of relapse after completion of treatment
- Malignant cells often comprise only a part of tumor mass – so conventional imaging has limitation in assessing response and residual disease – size reduction is not accurate predictor of response
- PET is functional imaging tool

TREATMENT

- Curable in majority of patients despite advanced stage
- Combination chemotherapy is standard of care for Classical Hodgkin's disease
- Number of courses of chemotherapy varies with stage
- Involved field radiotherapy is used following short course of chemotherapy in early stage Hodgkin's disease
- Role of radiotherapy is undergoing re-evaluation.
- Involved field radiotherapy is commonly used in Lymphocyte predominant subtype which typically presents in localized stage
- THREE PROGNOSTIC GROUPING
  - Early favorable
  - Early unfavorable
  - Late or advanced stage
- Early favorable
  - Stage IA and IIA – non bulky favorable
  - Short course of chemotherapy (2-4 cycles) followed by involved field radiation therapy (20 Gy)
  - Cure rate of 90-95%
- Early unfavorable
  - Stage I and II with bulky disease / Bulky disease :
    - More than 10 cm size or more than one third of trans-thoracic diameter
    - Sed rate over 50
    - More than three disease sites
    - B symptoms
    - Extra nodal disease
  - Six cycles of chemotherapy followed by involved field Radiation
  - Augmented regimen Stanford V or BEACOPP is used by some
- Advanced disease
  - Stage III and IV
  - Unfavorable features
  - up to 30% are at risk of death
  - ABVD is standard of care in United States
  - Role of consolidation RT in patients with stage III and IV disease remain controversial
  - ABVD is more effective and less toxic than MOPP
  - Full dose administration without delay, dose reduction or growth factor is necessary to optimize cure rates

- Stanford V and BEACOPP regimens are designed to reduce cumulative toxicity of several drugs and to improve outcomes
- BEACOPP regimen is used more commonly in Europe
- Stanford V and BEACOPP regimens are awaiting comparisons to ABVD
- MOPP:
  - Developed in 1960s
  - Rarely used now - because of toxicity
  - Increased risk of acute myeloid leukemia in survivors

RELAPSED HODGKIN"S LYMPHOMA

- 10-20% patient do not achieve CR or PR
- Another 15-30% relapse after initial CR
- Treatment:
  - Initial RT alone → ABVD results in long term disease free survival in 50-80%
  - Initial ABVD→ Salvage second line regimens (ICE, CHLVPP or Gemcitabine based) are used – 15% 5 year disease free survival
- High dose therapy and stem cell transplant
  - Considered standard for patient with relapse who remains sensitive to chemotherapy (in second CR)
  - 5 year relapse free survival is 20-50% based on prognostic factors
  - Likelihood of successful transplant is higher if ABVD was used as front line therapy rather than BEACOPP
  - Role of stem cell transplant in first CR remains controversial and not yet proven

Nodular Lymphocyte predominant Hodgkin's lymphoma - treatment

- Early stage / localized Nodular Lymphocyte predominant Hodgkin's lymphoma
  - Involved field RT is used for early stage local disease
  - Late relapses are common
  - Relapse/Recurrence after local RT:
    - Can be treated with additional RT (if outside radiation field)
    - or Single agent Rituximab (70-100% Response rate)
    - Or with combination ABVD
- Disseminated Nodular Lymphocyte predominant Hodgkin's lymphoma
  - Generally it is treated with ABVD.
  - Rituxan has been used successfully as well in some situations.

SPECIAL SITUATIONS

- Residual masses after treatment
  - Many patients with mediastinal and retro-peritoneal disease have residual masses
  - In many cases residual mass represents fibrosis
  - PET scan can help differentiate between active tumor and fibrosis
- Regenerating thymus
  - Regenerating thymus in young patients may create confusion because of increasing size of mediastinal mass – thymus can be positive on PET scan
  - Careful assessment is necessary in this situation

FOLLOW UP

- Purpose of long term follow up:
  - To monitor for relapse
  - To monitor for late effects of treatment
  - To monitor for new primary cancer
- Late effects of treatment
  - Myelo-dysplasia
    - RT alone or ABVD alone are generally associated with low risk
  - Treatment related secondary leukemia
    - ABVD: less than 1% risk of leukemia
  - Secondary diffuse non Hodgkin's lymphoma : rate of 4-5% at 10 years
- Secondary cancers
  - Solid tumor risk – 2% at 10 years and 13% at 19 years – about 22% at 25 years
  - RT is associated with increased risk of breast cancer, lung cancer, soft tissue sarcoma, melanoma in irradiated fields
  - Solid tumor risk after RT: 1% per year in smokers, 0.5% per year in non smokers
  - Breast cancers are often bilateral – start breast cancer and mammogram early
- Hypothyroidism is common after mantle filed RT – seen in two thirds
- Premature coronary artery disease risk is increased with Doxorubicin and mediastinal RT
- Pulmonary toxicity is seen after Bleomycin and mantle field RT
- Infertility:
  - MOPP/ alkylators almost always cause long term infertility
  - ABVD has low risk of long term infertility
- Modern RT may reduce risk of long term toxicity
- Avoiding alkylators may reduce risk of late toxicity

PROGNOSIS

- Overall prognosis is good with treatment
- See above under treatment section

SAMPLE QUESTIONS