HODGKIN’S LYMPHOMA (HODGKIN’S DISEASE)

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 sweats, 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 hepatosplenomegaly
  • 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 structure
- 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 diaphragm
- Stage IV: Disseminated disease (marrow, liver etc)

Substages:
- A: Absence of B symptoms;
- B: Presence of B symptoms (fever over 37°C on two occasions not related to infection, unintended loss of more than 10% body weight 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
  - 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:
  o To monitor for relapse
  o To monitor for late effects of treatment
  o To monitor for new primary cancer
• Late effects of treatment
  o Myelo-dysplasia
    • RT alone or ABVD alone are generally associated with low risk
  o Treatment related secondary leukemia
    • ABVD: less than 1% risk of leukemia
  o Secondary diffuse non Hodgkin’s lymphoma: rate of 4-5% at 10 years
• Secondary cancers
  o Solid tumor risk – 2% at 10 years and 13% at 19 years – about 22% at 25 years
  o RT is associated with increased risk of breast cancer, lung cancer, soft tissue sarcoma, melanoma in irradiated fields
  o Solid tumor risk after RT: 1% per year in smokers, 0.5% per year in non smokers
  o Breast cancers are often bilateral – start breast cancer and mammogram early
• Hypothyroidism is common after mantle field 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:
  o MOPP/ alkylators almost always cause long term infertility
  o 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