Hodgkin’s disease/lymphoma

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Characteristics of classical Hodgkin lymphoma

- Type of malignant lymphoma in which Reed-Sternberg cells are present in a characteristic background of reactive inflammatory cells of various types, accompanied by fibrosis of variable degree. (except NLPHL)
- Typically affects young people.
- Commonly presents with contiguous lymphadenopathy and/or a mediastinal mass; B symptoms and pruritus are also common.
- High cure rates with combination chemotherapy (with or without radiotherapy).
First described in 1832 by Dr. Thomas Hodgkin (1798-1866)

British physician, considered one of the most prominent pathologists of his time and a pioneer in preventive medicine. He is now best known for the first account of Hodgkin's disease, a form of lymphoma and blood disease, in 1832. Hodgkin's work marked the beginning of times when a pathologist was actively involved in the clinical process.
• Neoplasm of B cell lymphocytes – large prominent nucleolus in a halo – **Hodgkin cells**
• **Reed-Sternberg cell** – binucleate Hodgkin cell with owl eye appearance
• Classification (WHO 2008):
  Classical Hodgkin’s (95%)
    Nodular sclerosis – low grade
    Mixed cellularity
    Lymphocyte rich classical
    Lymphocyte depleted – high grade
  Nodular lymphocytoma predominant Hodgkin’s (5%)
Hodgkin lymphoma - Pathology

- Cell of origin: Germinal centre B-cell

- Reed-Sternberg cells (or RS variants) in the affected tissues

- Most cells in affected lymph node are polyclonal reactive lymphoid cells, not neoplastic cells. Neoplastic cells constitute only a small minority of the cells in the affected tissue, often corresponding to <2% of the total tumor
Reed-Sternberg Cells

- Large cells (>45um in diameter) with classically binucleate or bilobed nucleus each with a large acidophilic central nucleoli surrounded by a clear halo. "owl’s eye appearance"
- Variants: mononuclear (Hodgkin’s cell), mummified cell, lacunar cell, L/H cell.
- Requirement of RS cell for initial diagnosis is "absolute".
- Classic RS cell:
  + CD15, CD30, CD25
  - CD45, pan-B, S-100, keratin, EMA
- Most current studies indicate the RS cell of HL are lymphocytic in nature and, in great majority of cases, are of B-cell origin
CD 30 immunostain
Characteristics I.

• Bimodal age distribution:
  First peak between 2nd-3rd decade of life
  Second peak between 5th-6th decade of life
• Male:Female 2:1 in kids, adults most equal M:F
• Mixed cellularity (MC) HL is more common at younger ages.
• More common in immune deficiency patients.
Characteristics II.

• Past: Fatal disease with 90% of untreated patients dying within 2-3 years.
• With chemotherapy, >80% of patients suffering from HD are cured.
• Pathogenesis of HD is still largely unknown.
• HD nearly always arises and disseminates in lymph nodes.
Risk Factors

- No clear risk factors, several implicated
  - EBV (pathogen or passenger)
  - HIV
  - Woodworking, farming
  - Rare familial aggregations
- First degree relatives have five fold increase in risk for HL
- Associated with EBV infection mainly with mixed cellularity type
- High socio-economic status
- Prolonged use of human growth hormone
- Men>women
- Whites>Blacks>Asians
Clinical features, Clinical presentation

- Most common presentation is **asymptomatic lymphonode enlargement**, typically in the neck.
- **Cervical lymphonodes** are involved in 80% cases.
- **Mediastinal involvement** is seen in about 50% cases. They produce symptoms like chest pain, cough and dyspnoea.
- **Infradiaphragmatic involvement** is seen in 5% cases and usually seen with older patients.
- **Other symptoms** are: pruritus, fatigue, weakness, less common: alcohol induced pain over involved lymphonodes, abdominal pain, bowel disturbances, ascites, bone pain, nephrotic sy, erythema nodosum, cerebral degeneration, immunhaemolytic anaemia, thrombocytopenia, hypercalcaemia
- **Bone marrow** is involved in 5% of patients.
Interest tidbits

• Pel-Ebstein Fevers
• Pain with alcohol consumption
B symptoms

• About 33% present with B symptoms overall

1. Fever (>38°C)
   – May first present as fever of unknown origin (FUO)
   – Fever persists for days to weeks followed by afebrile intervals and then recurrence
   – This pattern is called Pel Ebstein fever

2. Drenching night sweats

3. Weight loss (>10% in 6 months)
Staging (Ann Arbor staging system)

Stage I: involvement of single lymph node region or single extralymphatic site (I_E)

Stage II: involvement of two or more lymph node regions on same side of diaphragm; may include localized extralymphatic

Stage III: involvement of lymph node regions on both sides of the diaphragm; may include spleen (III_S) or localized

Stage IV: diffuse extralymphatic disease (e.g. in liver, bone marrow, lung, skin)
Prognosis

**Early stage (I-II):**
- Age > 50y
- Involved regions > 3
- Bulky tumor
- ESR > 50mm/h A st, > 30mm/h B st

**Advanced stage (III-IV):**
- Age > 45
- Male
- Albumin < 40g/l
- Hemoglobin < 105
- WBC > 15G/l
- Lymphocytta < 0.6G/l or 8%

*Other important factors: ECOG performance status, concomittant diseases, compliance*
Diagnostic workup I.

- History
- Complete physical examination
- Confirmatory workup
  - Excisional biopsy of the lymphnode

**Staging**
- Chest X ray (PA, lat), ECG, Card. echo
- USG neck, abdomen
- CT scan thorax, abdomen, pelvis – FDG/PET CT
Diagnostic workup II.

Routine blood tests:
- Complete blood count
- Renal function
- Liver function
- Se. albumin
- ESR
- LDH
- Beta-2 microglobulin
Bone Marrow Biopsy

- Overall involvement of bone marrow in HL is 5%.
- Less commonly put into practice
- Indicated in pts with:
  - B symptoms
  - Clinical evidence of sub diaphragmatic disease
  - Stage III-IV
  - Recurrent disease
PET SCAN

- PET Scan has become an integral component of initial staging.

- Information provided by PET has been recently incorporated in the lymphoma guidelines for response evaluation after completion of treatment.

- Useful for follow up study to evaluate residual masses, dx of early recurrence and predicting outcome.

- It has a specificity of 90-95%
Treatment I.

General treatment principles include the following:

- Radiation therapy
- Induction chemotherapy
- Salvage chemotherapy
- Hematopoietic stem cell transplantation
- Immun-therapy
Treatment II.

The following induction regimens are given as initial treatment for Hodgkin lymphoma:

- **ABVD** (Adriamycin [doxorubicin], bleomycin, vinblastine, dacarbazine)
- **MOPP** (mechlorethamine, vincristine, procarbazine, prednisone)
- **Stanford V** (doxorubicin, vinblastine, mustard, bleomycin, vincristine, etoposide, prednisone)
- **BEACOPP** (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)
Treatment III.

When induction chemotherapy fails, or patients experience relapse, salvage chemotherapy is generally given. Salvage regimens incorporate drugs that are complementary to those that failed during induction therapy. Commonly used salvage regimens include the following:

- **ICE** (ifosfamide, carboplatin, etoposide)
- **DHAP** (cisplatin, cytarabine, prednisone)
- **ESHAP** (etoposide, methylprednisolone, cytarabine, cisplatin)
Treatment IV – ASCT, AlloSCT

- High-dose chemotherapy at doses that ablate the bone marrow is feasible with reinfusion of the patient's previously collected hematopoietic stem cells or infusion of stem cells from a donor source. Historically, hematopoietic stem cells have been obtained from bone marrow, but they are now typically obtained by pheresis of peripheral blood lymphocytes. A validated and relatively safe conditioning regimen for autologous transplantation is the BEAM regimen (carmustine [BCNU], etoposide, cytarabine, melphalan).

- ASCT can cure half of the refractor/relapsed patients.
Treatment V.

Immun-therapy:

• Brentuximab-vedotin - anti-CD30 Ab
• Nivolumab – PD1 inhibitor
Treatment VI.

- Because of a very high cure rate in patents with HL, long term complications should be taken into consideration and have become a major focus for clinical research:
  - Treatment – related second neoplasms (AML, NHL, breast cancer)
  - Infertility
  - Cardiac injury
  - Growth consideration
  - Long-term organ dysfunction (thyroid, heart, lung)
Summary – Main characteristics of classical Hodgkin lymphoma

- Typically affects young people.
- Commonly presents with contiguous lymphadenopathy and/or a mediastinal mass; B symptoms and pruritus are also common.
- High cure rates with combination chemotherapy (with or without radiotherapy).
- Late effects of therapy are an increasing concern (secondary cancer and heart disease).
- Pathology: Hodgkin/Reed-Sternberg cells in a reactive background.
- Immunophenotype: $\text{CD}15^+$, $\text{CD}30^+$, $\text{CD}19^-$, $\text{CD}20^-$, $\text{CD}79a^-$, $\text{CD}45^-$
Case 1 - simple

- 24y old female
- Anamnesis: negative
- Complains: dyspnoe, back pain, loosing weight
- Chest X ray, spine x ray: mediastinal broadening → CT: broad frontal mediastinum, inhomogenous tumor mass with necrosis, which dislocated and compressed the trachea, compressed the big mediastinal vessels, pericardial effusion
ÜLŐ HELYZETBEN, KILÉGZÉSBEN!
Case 1 - simple

- Supraclavicular and cervical lymphadenomegaly
- Pericardiocentesis (800ml)
- Supraclavicular lygl biopsy (intratracheal narcosis)
- Histology: Classical HL, nodular sclerosis
- PET/CT: supradiaphragmatic lymphadenomegaly, sternum and pericardium are involved, bulky disease (II B-E bulky)
- Th: ABVD, 6 cycles, profilactic LMWH till the interim PET/CT
- After the first cycle control X ray showed significant regression, cardiac usg was neg.
- Interim PET/CT (after 2nd cy): CMR
- After 6. cy.: final PET/CT neg.
- IFRT after the chemo, to complete the therapy (because of bulky disease)
- Regular ambulant control, hopefully cured
Case 2 – primer refracter

- 21y old female
- Anamnesis: asthma in childhood, this time not on treatment
- Complain: bilateral cervical lymphadenomegaly
- CT: generalised lymphadenomegaly, focal hepatic lesions, v. jug compression
- Cervic lygl biopsy: Classical HL, nodular sclerosis
- PET/CT: lygls on both sides of the diaphragm, focal hepatic, splenic and bone marrow lesions (IV/A-E st.)
- ABVD 6 cycles was planned
- Interim PET/CT (after 2nd cy): very significant regression, near CMR
- Final PET/CT: progression, new lesions
- Rebiopsy: the original histology
- DHAP salvage th.
- Stem cell harvesting after the 2nd cycle, than ASCT in case of remission.
- In case of residual disease: Brentuximab-Vedotin(+/-Bendamustin) to reach CMR before ASCT (the outcome after ASCT is much better in case of CMR!)
Case 3 – with many complications

- 39y old female
- Anamnesis: 18y – DVT, PE (contraceptive pill)
- Heterozigota Leiden mutation, antiphospholipid sy
- 2014.05. Dyspnoe → DVT, PE → LMWH, Acenocumarol
- 2014. PE
- 2016.01. Mediastinal relapsus, rebiopsy, histology the same
- 2016.02. I. DHAP. Bleeding symptoms and PLT<10 → stop anticoagulation → PE, Resp insuff., neuropathy, reversible renal insuff. (ICU)
- 2016.03. I. IGEV, keep PLT>20, on LMWH, righ heart insuff, pneumonia (ESBL Klebsiella) cardioresp. Insuff → ICU, mech. ventilation (6 days), iv. Imipenem, inhal. Gentamycin, anticoag: Na-Heparin
- 2016.04. Brentuximab (Adcetris) – Bendamustin (6 cycles)
- 2016.09. Stem cell harvesting
- PET/CT: MRD. Brentuximab till the ASCT (planned: 2017.01-02.)
Case 4 – relapsed after ASCT, problem with compliance

- 37y old female
- 2014.07.: Right supraclavicular lymphadenomegaly, fever, ESR ↑
- 2014.08. Biopsy: Classical HL, nodular sclerosis
- Staging PET/CT mediastinal and right supraclavicular lygls: II/B st.
- ABVD 4 cycles, interim PET/CT: CMR, ending PET/CT: CMR (2015.02.). Didn’t want to get irradiation.
- 2015.04.: Dysphagia, chest dyscomphort, 05. PET/CT: relapse (left supraclav., right hilar).
- I. DHAP salvage th. - resistant
- I-II. IGEV, stem cell harvesting after the 2. cy.
- 2 cy Brentuximab + 4 cy Brentuximab + Bendamustin
- 2016.04. ASCT
- 2016.08. Early relapse (cervical l.u., axillar l.s.)
- 2016.09. Brentuximab – Benda, than Nivolumab (2 years, „named patient program“)
Thank you for your attention