Relapsed and Refractory Hodgkin Lymphoma

Lymphoma Tumor Board

October 20, 2017
Thomas Hodgkin (1798-1866)
ON SOME
MORBID APPEARANCES
OF
THE ABSORBENT GLANDS
AND
SPLEEN.

BY DR. HODGKIN.

PRESENTED
BY DR. R. LEE.

READ JANUARY 10TH AND 24TH, 1832.

The morbid alterations of structure which I am about to describe are probably familiar to many practical morbid anatomists, since they can scarcely have failed to have fallen under their observation in the course of cadaveric inspection. They have not, as far as I am aware, been made the subject of special attention, on which account I am induced to bring forward a few cases in which they have occurred to myself, trusting that I shall at least escape severe or general censure, even though a sentence or two should be produced from some existing work, couched in such concise but expressive language, as to render needless the longer details with which I shall trespass on the time of my hearers.

CASE I.

November 2, 1826. Joseph Sinnott, a child of about nine years of age, in Lazarus’s ward, under the care of J. Morgan. His brother, his constant companion with whom he had habitually slept, died of phthisis a few months previously; he was much reduced by an illness of about nine months, during which time he had been subject to pain in the back, extending round to the abdomen. On his admission his belly was much distended with ascites. He had also effusion into the prepuce and scrotum. On the latter was a large ulcer induced by a puncture made to evacuate the fluid.

Head.—There was a considerable quantity of serious effusion under the arachnoid and within the ventricles. There were a few opaque spots in the arachnoid, but this membrane was in other respects healthy. The pia mater appeared remarkably thin and free from vessels. The substance of the brain was generally soft and flabby, but no local morbid change was observable.

Chest.—The pleura on the right side had contracted many strong and old adhesions, in addition to which there were extensive marks of recent pleuritis. On the left the pleura was nearly or quite free from adhesion, but there was some fluid effused into
Etiology - Hodgkin Lymphoma

**Infectious agents**
- EBV, may be involved in the pathogenesis. In as many as 50% of cases, the tumor cells are EBV-positive.
- Patients with HIV infection have a higher incidence of Hodgkin lymphoma compared with the population without HIV infection.

**Genetic predisposition**
- Approximately 1% of patients with Hodgkin lymphoma have a family history of the disease.

**UV radiation exposure**
- May have a protective effect against lymphomagenesis through mechanisms that may be independent of vitamin D

Subtypes of Classical Hodgkin Lymphoma (cHL)*

- Nodular sclerosing HL
  - Most common subtype
  - Composed of large tumor nodules
  - Nodules show scattered lacunar classical Reed Sternberg (RS) cells that are reactive
- Mixed-cellularity subtype
  - Common subtype
  - Composed of numerous classic RS cells with inflammatory cells
  - Frequently associated with EBV infection
  - Can be confused with “cellular” phase of nodular sclerosing CHL.
- Lymphocyte-rich
  - Rare subtype
  - Has most favorable prognosis
- Lymphocyte-depleted
  - Rare subtype
  - Composed of large numbers of pleomorphic RS cells with intermixed with reactive lymphocytes, which can be confused with DLBCL
- *~5% of patients have “nodular lymphocyte predominant Hodgkin lymphoma”
Staging of Hodgkin Lymphoma (HL)

- **Stage I**
  - Involvement of single lymph node region
  - Typically, cervical nodes or single extralymphatic site (stage IE)
- **Stage II**
  - Involvement of two or more lymph node regions on **same** side of diaphragm
  - One lymph node region and a contiguous extralymphatic site (IIE)
- **Stage III**
  - Involvement of two or more lymph node regions on both sides of the diaphragm
  - Can include spleen (IIIS) and/or limited contiguous extralymphatic organ sites (IIIIE, IIIES)
- **Stage IV**
  - Disseminated involvement of one or more extralymphatic organs
**HODGKIN LYMPHOMA STAGING**

**Table 1**

**Definitions of Stages in Hodgkin’s Disease**

**Stage I** Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (I_E).

**Stage II** Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its regional lymph node(s), with or without involvement of other lymph node regions on the same side of the diaphragm (II_E).

Note: The number of lymph node regions involved may be indicated by a subscript (eg, II_3).

**Stage III** Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an associated extralymphatic organ or site (III_E), by involvement of the spleen (III_S), or by both (III_E_S).

**Stage IV** Disseminated (multifocal) involvement of one or more extralymphatic organs, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

A  No systemic symptoms present
B  Unexplained fevers >38°C; drenching night sweats; or weight loss >10% of body weight (within 6 months prior to diagnosis)


PET scans are useful for upstaging in stage I-II disease. If there is PET positivity outside of disease already identified, further clinical investigation is recommended to confirm or refute the observation. PET scans are usually positive in patients with HIV infection, even in the absence of Hodgkin lymphoma.

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## Clinical Staging for Classical Hodgkin Lymphoma (CHL)\(^i\)

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Bulky Disease(^i) (mediastinal or peripheral)</th>
<th>Number of nodal sites(^i)</th>
<th>Erythrocyte sedimentation rate (ESR)</th>
<th>Guidelines Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>No</td>
<td>1</td>
<td>&lt;50</td>
<td>HODG-3 or HODG-4</td>
</tr>
<tr>
<td>IB</td>
<td>No</td>
<td>1</td>
<td>Any</td>
<td>HODG-6</td>
</tr>
<tr>
<td>IIA, no extralymphatic (E) lesions</td>
<td>No</td>
<td>&lt;3</td>
<td>&lt;50</td>
<td>HODG-3 or HODG-4</td>
</tr>
<tr>
<td>IIA ± extralymphatic (E) lesions</td>
<td>No</td>
<td>&lt;4</td>
<td>&lt;50</td>
<td>HODG-4</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>≥4 or</td>
<td>≥50</td>
<td>HODG-6</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Any</td>
<td>Any</td>
<td>HODG-7</td>
</tr>
<tr>
<td>IIB ± extralymphatic (E) lesions</td>
<td>No</td>
<td>Any</td>
<td>Any</td>
<td>HODG-6</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Any</td>
<td>Any</td>
<td>HODG-7</td>
</tr>
<tr>
<td>III-IV</td>
<td>Yes/No</td>
<td>Any</td>
<td>Any</td>
<td>HODG-10</td>
</tr>
</tbody>
</table>

\(^i\)For definitions of bulky disease and lymph node regions, see HODG-A.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Hodgkin Lymphoma (Age ≥18 years)

## Unfavorable Risk Factors for Stage I-II Classical Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>GHSG</th>
<th>EORTC</th>
<th>NCCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥50</td>
<td>≥50 or any B symptoms</td>
<td>≥50 or any B symptoms</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR and B symptoms</td>
<td>&gt;50 if A; &gt;30 if B</td>
<td>&gt;50 if A; &gt;30 if B</td>
<td>&gt;50 or any B symptoms</td>
</tr>
<tr>
<td>Mediastinal mass</td>
<td>MMR &gt; .33</td>
<td>MTR &gt; .35</td>
<td>MMR &gt; .33</td>
</tr>
<tr>
<td># Nodal mass sites</td>
<td>&gt;2*</td>
<td>&gt;3*</td>
<td>3</td>
</tr>
<tr>
<td>E lesion sites</td>
<td>any</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulky</td>
<td>≥10 cm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GHSG = German Hodgkin Study Group**  
**EORTC = European Organization for the Research and Treatment of Cancer**  
**MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter**  
**MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5-6**

## Definitions of Lymph Node Regions*

<table>
<thead>
<tr>
<th>Region</th>
<th>Ann Arbor</th>
<th>EORTC</th>
<th>GHSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Cervical/SCL</td>
<td>R Cervical/SCL</td>
<td>R Cervical/SCL</td>
<td>R Cervical/SCL</td>
</tr>
<tr>
<td>R ICL/Subpec</td>
<td>R ICL/Subpec</td>
<td>R ICL/Subpec</td>
<td>R ICL/Subpec</td>
</tr>
<tr>
<td>R Axilla</td>
<td>R Axilla</td>
<td>R Axilla</td>
<td>R Axilla</td>
</tr>
<tr>
<td>L Cervical/SCL</td>
<td>L Cervical/SCL</td>
<td>L Cervical/SCL</td>
<td>L Cervical/SCL</td>
</tr>
<tr>
<td>L ICL/Subpec</td>
<td>L ICL/Subpec</td>
<td>L ICL/Subpec</td>
<td>L ICL/Subpec</td>
</tr>
<tr>
<td>L Axilla</td>
<td>L Axilla</td>
<td>L Axilla</td>
<td>L Axilla</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>Mediastinum</td>
<td>Mediastinum</td>
<td>Mediastinum</td>
</tr>
<tr>
<td>R Hilum</td>
<td>R Hilum</td>
<td>R Hilum</td>
<td>R Hilum</td>
</tr>
<tr>
<td>L Hilum</td>
<td>L Hilum</td>
<td>L Hilum</td>
<td>L Hilum</td>
</tr>
</tbody>
</table>

| Total           | 9         | 5      | 5     |

*Note that the EORTC includes the infraclavicular/subpectoral area with the axilla while the GHSG includes it with the cervical. Both EORTC and GHSG combine the mediastinum and bilateral hilum as a single region.

## International Prognostic Score (IPS)

1 point per factor (advanced disease)†

- Albumin < 4 g/dL
- Hemoglobin < 10.5 g/dL
- Male
- Age ≥45 years
- Stage IV disease
- Leukocytosis (white blood cell count at least 15,000/mm3)
- Lymphocytopenia (lymphocyte count less than 8% of white blood cell count, and/or lymphocyte count less than 600/mm3)


---

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

---

**Version 2.2016, 04/29/16 © National Comprehensive Cancer Network, Inc. 2016. All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

---

HODG-A
Classic Hodgkin lymphoma – Reed-Sternberg Cell Variants

Classic RS Cell

Lacunar Cells

Mummified Cell

Emily Glynn

Hsi ED and Golblum JR. Foundations in Diagnostic Pathology: Hematopathology. 2nd Ed. 2012
Classical Hodgkin Lymphoma - Immunophenotype
Genetic and Immunohistochemical Analyses of PDL1 and PDL2 Loci, PD-L1 and PD-L2 Protein Expression, and Epstein–Barr Virus Status in Patients with Hodgkin Lymphoma

![Genetic and Immunohistochemical Analyses](image)

**Table D**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Cytogenetic Alterations</th>
<th>IHC-positive HRS cells</th>
<th>Nuclear pSTAT3</th>
<th>EBER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Polysomy 9p</td>
<td>PDL1/2 Gain</td>
<td>PDL1/2 Amplification</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Deauville Scoring System

- Internationally accepted and utilized five-point scoring system for the fluorodeoxyglucose (FDG) avidity of Hodgkin’s lymphoma or NHL tumor mass seen on FDG PET.
- Scores of 1 and 2 are considered to be negative and 4 and 5 are considered to be positive. "Score 3 should be interpreted according to the clinical context but in many Hodgkin Lymphoma patients indicates a good prognosis with standard treatment."

### Table 2.

Deauville 5-point scoring system.

<table>
<thead>
<tr>
<th>Score</th>
<th>Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No uptake</td>
</tr>
<tr>
<td>2</td>
<td>Uptake &lt; mediastinum</td>
</tr>
<tr>
<td>3</td>
<td>Uptake &gt; mediastinum but &lt; liver</td>
</tr>
<tr>
<td>4</td>
<td>Uptake moderately more than liver, at any site</td>
</tr>
<tr>
<td>5</td>
<td>Markedly increased uptake at any site and/or new sites of disease</td>
</tr>
</tbody>
</table>
Treatment of limited stage Hodgkin lymphoma

Treatment of advanced stage Hodgkin lymphoma (1)

• Depends on patient age, performance status, stage of disease (limited/advanced), and patient preference

First Line Therapy – Advanced Stage Disease

• **ABVD** - Adriamycin, bleomycin, vinblastine, and dacarbazine
• Standard treatment of HL in the US
• Takes ~6 months
• **MOPP** – [Nitrogen] Mustard, Oncovin, Prednisone and Procarbazine
• Administered in four week cycles, often for 6 cycles.
• Not often used, but a reasonable option for those with relapse or other complications.
• **Stanford V regimen** - typically takes half as long as ABVD, but more intense chemotherapy schedule, and incorporates radiation.
• **BEACOPP** - treatment for stages > II, mainly used in Europe
• Approximately 10-15% higher with standard ABVD in advanced stages.
• More expensive due to use of G-CSF, more intense and more toxic
• Rituximab is not routinely used due to lack of CD20 surface expression on RS cells
Treatment of advanced stage Hodgkin lymphoma (2)

Second Line Therapy – Advanced Stage Disease

• **ICE**: Ifosfamide (Ifex), carboplatin (Paraplatin), and etoposide
  - Given every 2 or 3 weeks for 2-4 cycles.

• **ESHAP or DHAP**: Etoposide, methylprednisolone (Solu-Medrol), high-dose cytarabine, (Cytosar-U), cisplatin (Platinol);
  - OR, dexamethasone, high-dose cytarabine, and cisplatin.
  - ESHAP or DHAP regimens are given every 3 weeks for 2 to 3 months.

• **GVD, Gem-Ox, or GDP**: Gemcitabine (Gemzar), vinorelbine (Navelbine), doxorubicin;
  - OR gemcitabine and oxaliplatin (Eloxatin);
  - OR gemcitabine, dexamethasone, and cisplatin.
  - Gemcitabine-based regimens are either given 2 weeks in a row, followed by an off-week, or every other week.

• **Brentuximab vedotin (Adcetris)**: Brentuximab vedotin (Adcetris) is an antibody-drug conjugate – anti-CD30 coupled to monomethyl auristatin A
  - Brentuximab vedotin is usually given every 3 weeks for up to 16 cycles, although sometimes it is given every 4 weeks.
Hodgkin Lymphoma (Age ≥18 years)

CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma
Stage III-IV

PRIMARY TREATMENT

ABVD x 2 cycles
or
Stanford V x 12 weeks (in selected patients if IPS <3)

Deauville 1.3°
→ ABVD x 4 cycles (total 6)
or
AVD x 4 cycles

Restage with PET/CT

or

Consider escalated BEACOPP x 4 cycles (See HODG-12)

Deauville 4.5°

Deauville 1.3°
→ ISRT to initially bulky or selected PET+ sites

Consider ISRT to PET+ sites (Deauville 4)

Positive
→ See Refractory Disease

Negative
→ Observe or ISRT to initially bulky or PET+ sites

→ See Follow-up

Deauville 4.5°

Deauville 1.3°
→ Observe

Escalated BEACOPP x 6 cycles (in selected patients if IPS ≥4, age <60)

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Classification of relapsed/refractory Hodgkin lymphoma

Table 1.

Classification of patients with relapsed and refractory HL in three risk groups: LYSA recommendations.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Prognostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk</td>
<td>Primary refractory disease(^1) or relapse with two poor prognosis factors (early relapse(^2) and stage III/IV at relapse)</td>
</tr>
<tr>
<td>Intermediate-risk</td>
<td>Relapse with only one poor prognostic factor (early relapse or stage III/IV at relapse)</td>
</tr>
<tr>
<td>Standard-risk</td>
<td>Relapse without risk factor (relapse &gt; 12 months after end of treatment and stage I/II disease)</td>
</tr>
</tbody>
</table>

\(^1\)Defined either by progression at any time during chemotherapy and up to 3 months after end of chemotherapy, or by failure to achieve at least PR with first-line therapy, or by persistence of significant (score 4 or 5/5) residual FDG metabolic activity using the quantitative 5-point scale Deauville score (DS). \(^2\)Defined by time to treatment failure > 3 months but < 12 months after end of first-line therapy.
Treatment of relapsed/refractory Hodgkin lymphoma (3)

**FIGURE.** Evidence-Based Uses of PET/CT in Relapsed or Refractory Hodgkin Lymphoma

- **Initial Diagnosis**
  - Frontline Therapy
  - Biopsy
    - Biopsy Negative: Surveillance PET/CT or Repeat Biopsy
    - Biopsy Positive: Relapsed/Refractory HL
  - End-of-Treatment PET/CT
    - Negative PET/CT
    - Positive PET/CT
  - Surveillance without PET/CT
- **Salvage Therapy**
  - End-of-Treatment PET/CT
  - Positive PET/CT: Unfavorable Clinical Trials or Escalation of Therapy
  - Negative PET/CT: Favorable
- **Auto SCT**
- **Post-treatment PET/CT**
  - Positive PET/CT: Unfavorable
    - Salvage Chemo, Brentuximab, or Allogeneic SCT
  - Negative PET/CT: Favorable

*AJHO. 2016;12(9):8-13*
Definition of response to salvage chemotherapy: recommendations by the LySA HL committee

- Response evaluation by CT scan with contrast dye if not contra-indicated
  - Complete response
  - Persisting mass
    - FDG-PET imaging interpreted using 5-point scale Deauville score
      - Score 1-3: Chemosensitive
      - Score 4-5: Chemoresistant

©2013 by Ferrata Storti Foundation
Eric Van Den Neste et al. *Haematologica* 2013;98:1185-1195
Selected studies of Brentuximab Vedotin informing treatment of relapsed/refractory HL at different disease stages

A

KEY
Selected references:
Authors, (Reference #)

Moskowitz et al, (34);
Chen et al, (35);
Moskowitz et al, (36);
LaCasce et al, (38)

Moskowitz et al, (19)

Younes et al, (7);
Gopal et al, (11);
Chen et al, (22);
Anderlini et al, (23);
Bartlett et al, (17)

Gopal et al, (28)

Diagnosis HL

Upfront therapy

Relapse/Refractory

Salvage therapy

Auto-SCT

Cure

Maintenance therapy*

Salvage therapy

Allo-SCT

Relapse/Refractory

Cure

B

HL

Cure

©2014 by American Society of Hematology

Response Characteristics and Changes in Tumor Burden in Patients with Hodgkin Lymphoma Receiving Nivolumab

Cumulative incidence of cause-specific mortality in long-term HL survivors

Andrea K. Ng Blood 2014;124:3373-3379

©2014 by American Society of Hematology
References

- https://en.wikipedia.org/wiki/Reed%E2%80%93Sternberg_cell
- http://slideplayer.com/slide/5990917/
- J. Shekeab , PET/CT in the Evaluation of Relapsed or Refractory Hodgkin Lymphoma. AJHO. 2016;12(9):8-13
- A. Gopal., Treatment of relapsed classical Hodgkin lymphoma in the brentuximab vedotin era. DOI: 10.1182/asheducation-2014.1.151