Hodgkin's Lymphoma

Oncology and Hematology · Part 4 – Oncology: Hematologic Malignancies

KEY CLINICAL POINTS

1. Hodgkin's lymphoma (HL) is a malignancy of mature B lymphocytes, representing ~10% of all lymphomas.
2. Classical Hodgkin's lymphoma (cHL) is the majority subtype; Nodular lymphocyte-predominant HL (NLPHL) is biologically related to indolent B-cell NHLs.
3. HL has a bimodal age distribution with peaks in the 20s and 80s.
4. Reed-Sternberg (RS) cells are diagnostic, large with bilobed nuclei, expressing CD15 and CD30 (<1% of tumor cellularity).
5. 97% have PD-1L locus aberrations leading to immune suppression.
6. B symptoms (fever >38°C, night sweats, weight loss >10%) are prognostic factors in staging.
7. Pain in lymph nodes on alcohol ingestion is a characteristic finding in HL.
8. Early-stage disease (Stage I-II) treated with ABVD chemotherapy (4-6 cycles) ± radiation; 5-year OS ~97-100%.
9. Advanced-stage disease (Stage III-IV) treated with ABVD or AVD ± radiation.
10. Relapsed disease treated with salvage chemotherapy (ICE, GND) + autologous stem cell transplantation and immune checkpoint inhibitors (nivolumab, pembrolizumab).
11. International Prognostic Score (IPS) predicts survival based on 7 risk factors in advanced-stage disease.
12. EBV is detected in nearly all cases of HIV-associated cHL.

1. DEFINITION & OVERVIEW

- **Definition:** Hodgkin's lymphoma (HL) is a malignancy of mature B lymphocytes, representing ~10% of all lymphomas.
- **Subtypes:**
  - Classical Hodgkin's lymphoma (cHL): The majority subtype; cure rates >85% due to advances in chemotherapy and radiation therapy.
  - Nodular lymphocyte-predominant HL (NLPHL): Biologically related to indolent B-cell NHLs.

1.1 Subtypes of Hodgkin's Lymphoma

- **WHO Classification (Table 114-1):**
  - Nodular lymphocyte-predominant Hodgkin's lymphoma
  - Classical Hodgkin's lymphoma (cHL):
  - Nodular sclerosis (common in younger patients)
  - Lymphocyte-rich
  - Mixed cellularity (more common in elderly, HIV+, and developing countries)

- Lymphocyte-depleted
- **Note:** Nodular sclerosis and mixed-cellularity account for ~95% of cases.

TABLE 114-1

World Health Organization Classification of Hodgkin's Lymphoma

Classification	Subtypes
Nodular lymphocyte-predominant Hodgkin's lymphoma	Nodular lymphocyte-predominant Hodgkin's lymphoma
Classical Hodgkin's lymphoma	Nodular sclerosis, Lymphocyte-rich, Mixed cellularity, Lymphocyte-depleted

2. EPIDEMIOLOGY

- **Incidence:** Stable; ~8830 new cases in the US (2023).
- **Demographics:** More common in whites and males.
- **Age Distribution:** Bimodal distribution with peaks in the 20s and 80s.
- **Presentation:** Over two-thirds present with localized disease.

2.1 Risk Factors

- **HIV Infection:** Increases HL risk.
- **EBV Association:** EBV is detected in ~100% of HIV-associated cHL vs. ~33% of non-HIV cases.

3. ETIOLOGY & PATHOPHYSIOLOGY

- **Reed-Sternberg (RS) Cells:**
  - Diagnostic hallmark; large cells with bilobed nuclei and abundant cytoplasm.
  - Markers: CD15+ and CD30+.
  - Prevalence: <1% of tumor cellularity.
- **Immune Evasion:**
  - RS cells interact with the microenvironment via cytokines to evade immune destruction.
  - 97% have PD-L1 locus aberrations leading to immune suppression.

3.1 EBV and HIV Association

- **EBV Role:** Implicated in HL pathogenesis, particularly in HIV-associated cases.
  - EBV genomes are episomal and clonal in HIV-related cHL, suggesting a direct oncogenic role.
  - RS cells in these cases express LMP-1 (EBV-transforming protein).

4. CLINICAL FEATURES

- **Primary Presentation:** Palpable lymphadenopathy (neck, supraclavicular, axilla) and mediastinal adenopathy.
- **B Symptoms:** Occur in ~1/3 of cases; used as prognostic factors.
  - Fever >38°C
  - Night sweats

- Weight loss >10%

- **Other Manifestations:**
  - Pel-Ebstein fever (intermittent fevers).
  - Severe itching.
  - Cutaneous disorders (erythema nodosum, ichthyosiform atrophy).
  - Paraneoplastic cerebellar degeneration.
  - Nephrotic syndrome.
  - Immune hemolytic anemia/thrombocytopenia.
  - Hypercalcemia.
  - Alcohol-induced lymph node pain (characteristic finding).

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5. DIFFERENTIAL DIAGNOSIS

- **Mimickers:**
  - Inflammatory processes.
  - Mononucleosis.
  - Non-Hodgkin's lymphoma (NHL).
  - Phenytoin-induced adenopathy.
  - Nonlymphomatous malignancies.

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6. INVESTIGATIONS & DIAGNOSIS

1. **Histopathology:** Expert hematopathologist review of biopsy specimens to identify RS cells (bilobed nuclei, CD15+, CD30+; <1% tumor cellularity).
2. **Staging:** PET/CT is preferred for staging over bone marrow biopsy due to patchy marrow involvement.
3. **Ann Arbor Staging System (Table 114-2):**
   - Stage I: Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring).
   - Stage II: Involvement of ≥2 regions on same diaphragm side.
   - Stage III: Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm.
   - Stage III1: Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac nodes, or portal nodes.
   - Stage III2: Subdiaphragmatic involvement includes paraaortic, iliac, or mesenteric nodes plus structures in III1.
   - E: Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow.

6.1 Diagnostic Criteria

- **RS Cells:** Bilobed nuclei, CD15+, CD30+ (<1% tumor cellularity).
- **Imaging:** PET/CT preferred for bone marrow assessment.

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7. MANAGEMENT & TREATMENT

1. **Early-Stage Disease (I-II):**
   - Treatment: ABVD chemotherapy (4-6 cycles) ± radiation.

- 5-year OS: ~97-100%.
- **Risk Stratification (Table 7.1):**
  - Low-risk/Favorable → ABVD, No radiation (or IFRT 30 Gy), 4-6 cycles.
  - Good-risk → ABVD, Low-dose radiation (20 Gy), 2 cycles.
  - Bulky Disease → ABVD, Involved Field radiation, 6+ cycles.
- **Monitoring:** PET/CT after 2-3 cycles may guide treatment duration.

2. **Advanced-Stage Disease (III-IV):**
   - Treatment: ABVD or AVD (Brentuximab vedotin + doxorubicin, vinblastine, dacarbazine) for 6 cycles.
   - **Brentuximab:** CD30-targeting ADC; provides benefit in advanced disease.
3. **Relapsed/Refractory Disease:**
   - Salvage Chemotherapy: ICE or GND.
   - Consolidation: Autologous stem cell transplantation.
   - Advanced Options: Immune checkpoint inhibitors (nivolumab, pembrolizumab) and CAR T-cell therapy for multiply relapsed cHL.

7.1 Early-Stage Treatment Options

See Table 7.1 for risk-stratified treatment pathways.

TABLE 7

1 Early-Stage HL Treatment Options

Risk Category	Regimen	Radiation	Cycles
Low-risk/Favorable	ABVD	None (or IFRT 30 Gy)	4-6
Good-risk	ABVD	Low-dose (20 Gy)	2
Bulky Disease	ABVD	Involved Field	6+

7.2 Advanced-Stage Treatment Options

See Table 7.2 for advanced-stage regimens.

TABLE 7

2 Advanced-Stage HL Regimens

Regimen	Components	Notes
ABVD	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine	Standard of care
AVD	Brentuximab vedotin + doxorubicin, vinblastine, dacarbazine	CD30-targeting ADC

8. PROGNOSIS & COMPLICATIONS

- **Prognostic Factors:** B symptoms, bulky disease, ESR, and age.
- **International Prognostic Score (IPS) for Advanced Stage (Table 8.1):**

- Risk Factors (each = 1 point):
- Male sex
- Age >45 years
- Stage IV
- Albumin <4 g/dL
- Hemoglobin <10.5 g/dL
- WBC ≥ 15,000/μL
- Lymphocytes <600/μL or <8%
- Outcome: 5-year PFS 88% (no risk factors) to 62% (≥ 4 factors).

- **Late Toxicity:**
  - Secondary malignancies.
  - Cardiovascular disease (premature CAD, stroke).
  - Thyroid dysfunction.

8.1 International Prognostic Score (IPS) Criteria

See Table 8.1 for specific criteria.

TABLE 8

1 International Prognostic Score (IPS) Criteria

Risk Factor	Criteria	Points
Sex	Male	1
Age	>45 years	1
Stage	Stage IV	1
Albumin	<4 g/dL	1
Hemoglobin	<10.5 g/dL	1
WBC	≥ 15,000/μL	1
Lymphocytes	<600/μL or <8%	1

9. SPECIAL CONSIDERATIONS

- **HIV-Associated HL:**
  - Risk: Increased risk of HL in HIV patients.
  - EBV Status: Detected in nearly all cases (~100%).
  - Molecular: RS cells express LMP-1; EBV genomes are episomal and clonal.

10. KEY PEARLS & CLINICAL TRAPS

- **High Cure Rates:** >85% with modern therapy.
- **Diagnostic Hallmark:** RS cells (bilobed, CD15+, CD30+; <1% cellularity).
- **Staging Preference:** PET/CT is superior to bone marrow biopsy for assessing marrow involvement.
- **Clinical Clue:** Alcohol-induced lymph node pain is highly characteristic of HL.

- **Prognostic Value:** B symptoms are key indicators for staging and prognosis.
- **Advanced Therapy:** Immune checkpoint inhibitors show high response rates in relapsed disease.

Board Exam Favorites

- Bimodal age distribution (20s and 80s).
- RS cells: CD15+/CD30+ (<1% tumor cellularity).
- IPS criteria for advanced-stage prognosis.
- ABVD as standard regimen for early-stage disease.

REFERENCE TABLES

TABLE 114-1

World Health Organization Classification of Hodgkin's Lymphoma Nodular lymphocyte-predominant Hodgkin's lymphoma...

- Nodular lymphocyte-predominant Hodgkin's lymphoma
- Classical Hodgkin's lymphoma
- Nodular sclerosis
- Lymphocyte-rich
- Mixed cellularity
- Lymphocyte-depleted

TABLE 114-2

The Ann Arbor Staging System for Hodgkin's Lymphoma STAGE I II

STAGE	DEFINITION
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
III	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm
III 1	Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac nodes, or portal nodes
III 2	Subdiaphragmatic involvement includes paraaortic, iliac, or mesenteric nodes plus structures in III 1
A	No symptoms
E	Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow